DOCTOR OF MEDICINE

Using B-type natriuretic peptide and whole body contrast enhanced magnetic resonance imaging to detect asymptomatic cardiovascular disease and improve prediction of risk of cardiovascular disease
the TASCFORCE Study

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Using B-type natriuretic peptide and whole body contrast enhanced magnetic resonance imaging to detect asymptomatic cardiovascular disease and improve prediction of risk of cardiovascular disease: the TASCFORCE Study

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Abbreviations

AF = atrial fibrillation

ANP = atrial (A-type) natriuretic peptide

ASSIGN = Assessing cardiovascular risk using SIGN guidelines to assign preventive treatment

ATPIII = adult treatment panel III

AUC = area under the curve

BHS = British Hypertension Society

BMI = Body Mass Index

BNF = British National Formulary

BNP = B-type natriuretic peptide

BP = Blood Pressure

BSA = Body Surface Area

CAD = Coronary Artery Disease

CHD = Coronary Heart Disease

CHI = Community Health Index

CI = Confidence Interval

C-IMT = Carotid Intima Media Thickness

CMR = Cardiac Magnetic Resonance Imaging

CRF = Case Report Form

CRP = C-reactive protein

CT = Computed Tomography

CV = Cardiovascular

CVD = Cardiovascular Disease

DBP = Diastolic Blood Pressure

DE-MRI = Delayed Enhancement Magnetic Resonance Imaging

ECG = Electrocardiogram

FLASH = Fast low-angle shot

FOV = Field of View

GP = General Practice

GRAPPA = Generalised Autocalibrating Partially Parallel Acquisition

GRO = General Registrar Office

HDL = High Density Lipoprotein

HIC = Health Informatics Centre

hs = high sensitivity

ICD-10 = International Classification of Diseases version 10

IQR = Inter-quartile Range

ISD = Information and Statistics Division

LDL = Low Density Lipoprotein

LGE = Late Gadolinium Enhancement

LV = Left Ventricular

LVEF = Left Ventricular Ejection Fraction

LVEDV = Left Ventricular End Diastolic Volume

LVESF = Left Ventricular End Systolic Volume

LVM = Left Ventricular Mass

LVMI = Indexed Left Ventricular Mass

LVH = Left Ventricular Hypertrophy

MI = Myocardial Infarction

MIP = Maximum Intensity Projections

ML = Matthew Lambert

MMSE = Mini Mental State Examination

MPR = Multiplanar Reconstructions

MRI = Magnetic Resonance Imaging

MRA = Magnetic Resonance Angiography

NICE = National Institute of Health and Care Excellence

NT-proBNP = N-terminal proBNP

OPCS-4 = Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (4^{th} revision)

OR = Odds Ratio

PAD = Peripheral Arterial Disease

PSIR = Phase-Sensitive Inversion Recovery

QOF = Quality and Outcomes Framework

RANKL/OPG = Receptor activator of nuclear factor kappa-B ligand/osteoprotegerin

ROC = Receiver Operating Characteristic

ROI = Region of Interest

RR = Risk Ratio

SAS = Standardised Atheroma Score

SBP = Systolic Blood Pressure

SD = Standard Deviation

SIGN = Scottish Intercollegiate Guidelines Network

SIMD = Scottish Index of Multiple Deprivation

SSFP = Steady State Free Precision

TGE = Turbo Gradient Echo

TrueFISP = True fast imaging with steady state precision

WBAS = Whole Body Atheroma Score

WB CE-MRA = Whole Body Contrast Enhanced Magnetic Resonance Angiography

WB CE-MRI = Whole Body Contrast Enhanced Magnetic Resonance Imaging

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Declaration

I hereby declare that I am the author of this thesis, that all references cited have been consulted by me, and that I have carried out the work described in this thesis. The work described in this thesis has not been previously accepted for a higher degree and I have defined the nature of my contribution to the work within the project described in the thesis.

I contributed to the study design, was key in the running of the study, and designed the amendments to the study to improve its quality. I designed the statistical package, in collaboration with the study statistician. I analysed the data, again in collaboration with the study statistician, and I drew the study conclusions. I was responsible for the data linkage concept through the Health Informatics Centre and for the comparison of different risk scores. I checked the database for accuracy and corrected data entry errors in the database using the CRFs where required. I was lead author of the baseline paper (The Tayside Screening For Cardiac Events (TASCFORCE) Study: A Prospective Cardiovascular Risk Screening Study. Study aims, design and baseline characteristics) and have been co-author for a number of further papers which have been submitted for publication.

The work contained within this was carried out during my appointment as a Clinical lecturer in the Division of Cardiovascular and Diabetes Medicine, Medical Research Institute, University of Dundee, between September 2010 and August 2015.

Signed:……..

Dated:……

Summary

Cardiovascular disease remains a leading a cause of mortality and morbidity. Primary prevention is known to reduce the incidence of cardiovascular disease. The use of medication is currently targeted at those at increased predicted risk of cardiovascular disease using risk prediction tools developed from large epidemiological studies. However these have poor external validity particularly for those at low or intermediate risk: a significant number of cardiovascular events still occurs in these groups. We hypothesised that screening for asymptomatic pre-clinical cardiovascular disease using B-type natriuretic peptide (BNP) and whole body contrast enhanced magnetic resonance imaging (MRI) could identify those at low/intermediate risk or disease who will develop clinical disease and thus facilitate improved targeting of primary prevention at those most likely to benefit.

The Tayside Screening for Cardiac Events (TASCFORCE) study is a prospective normal volunteer cohort study. Men and women aged 40 years or older free from cardiovascular disease and with a predicted 10-year coronary heart disease risk less than 20% were recruited. All had comprehensive baseline cardiovascular risk information and a BNP level measured. If the BNP level was greater than the median for their gender participants were invited to attend for a whole body contrast enhanced MRI scan comprising cardiac imaging and whole body angiography. The images were analysed to measure left ventricular mass (LVM), left ventricular volumes and left ventricular function. These were indexed for body size using height, $height^{1.7}$, $height^{2.7}$ and body surface area. Angiogram images were analysed for the presence and degree of intraluminal stenosis. All participants are being followed up using anonymised electronic data linkage for incident cardiovascular disease and death.

4423 participants (39.3% male) were recruited between November 2007 and February 2013. Median age was 51.2 years. The median 10-year coronary heart disease (CHD)

risk was 2% and 13.6% had a CHD risk of 10-19.9% (intermediate risk). The median BNP results for men and women were 7.5 and 15.3 pg/ml respectively. Age, female sex and high density lipoprotein were independently associated with BNP level. Heart rate, total cholesterol and ex-smoking status were independently inversely associated with BNP level. 1528 (74.8% of those invited) underwent an MRI scan. Mean left ventricular mass was 129.2g and 87.0g for men and women respectively. LVM and left ventricular mass index (LVMI) were significantly higher in men than women. The vast majority (94.6%) of arterial segments analysed were normal and 50.6% of individuals had no evidence of luminal stenosis. From follow up data obtained 2 years after the end of recruitment 18,364 person years at risk were analysed. 17 cardiovascular events and no deaths occurred in those not invited for an MRI scan based on their BNP result and 16 events and 1 death occurred in those invited for an MRI scan. There was no significant difference in event rates between those with above and below median BNP levels, between those with higher or lower LVM or LVMI or between those with and without the presence of stenosis on angiography.

As expected we have not demonstrated the ability of LVM, LVMI or stenosis burden determined using magnetic resonance imaging to predict cardiovascular disease in a population at low or intermediate risk of CHD. We have also not demonstrated the ability of BNP to identify those at low or intermediate risk of CHD who will develop clinical CV disease. However it is the pre-planned longer-term follow up where difference might be expected. The low number of events at this early stage in follow up mean that it is difficult to draw firm conclusions. As follow up continues and further events accumulate we hope to determine if these measures will be shown to predict cardiovascular events in future analyses. We have characterised the normal values and distribution of a range of left ventricular structural and functional parameters derived using a steady state free precision sequence MRI in a population at low or intermediate risk of CHD which will provide a useful reference for normal values that

are different to other imaging modalities including echocardiography and other protocols of MRI scanning.

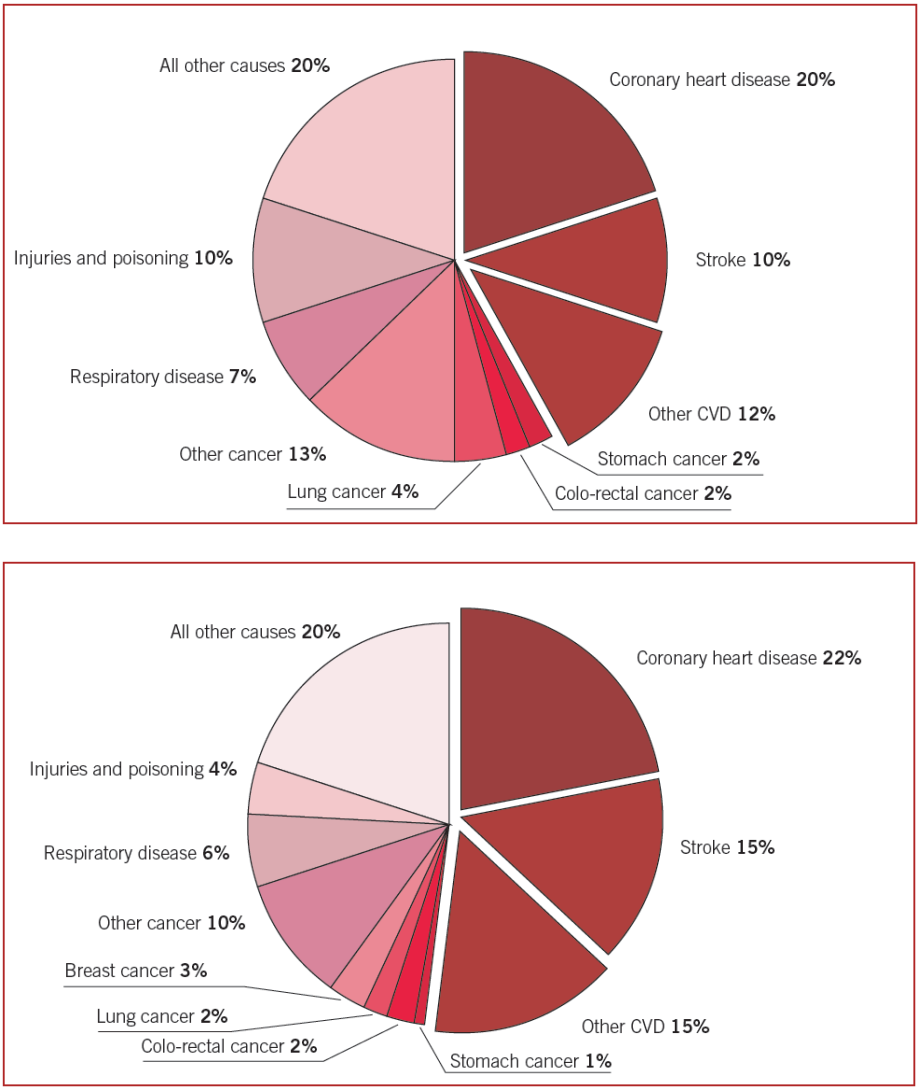
1. Literature review

1.1. Cardiovascular disease

1.1.1. The burden of cardiovascular disease

Cardiovascular disease (CVD) is a leading cause of mortality and morbidity in developed societies. It causes 47% of all deaths in Europe and 40% in the European Union (figure 1.1).[1] In Scotland myocardial infarction, stroke and peripheral arterial disease combined are responsible for more than 18500 deaths annually.[2]

Figure 1.1: Deaths by cause in Europe (men top, women bottom). Taken from European Cardiovascular disease statistics 2012.[1]



It is also a major cause of morbidity. Advances in medical therapy mean that many who would previously have died from cardiovascular events such as myocardial infarction or stroke now survive but live with either the effects of their acute event or live with chronic cardiovascular disease such as angina, peripheral arterial disease or heart failure. These produce a burden on both health and social care services. CVD is estimated to cost the European Union about €196 billion per year with 54% due to healthcare costs, 24% due to productivity losses and 22% for informal care for people with CVD.[1] As survival improves more people are also surviving long enough to develop other cardiovascular diseases such as vascular dementia increasing the demands on the health and social care systems further. It is estimated that over 815,000 people in the UK are currently living with dementia 17% (approx. 139,000) of whom have vascular dementia and 10% (approx. 81,000) have mixed dementia.[3] The total cost of all dementia to society in the UK (of which vascular dementia is a significant proportion) is estimated to be £26.3 billion of which £4.3 billion is for healthcare, £10.3 billion is for social care and £11.6 billion is contributed by unpaid carers of people with dementia.[3]

Therefore any steps to reduce the incidence of the range of cardiovascular diseases has the potential to reduce demand on the health and social care systems.

1.1.2. Pathophysiology of atherosclerosis

Atherosclerosis is a degenerative inflammatory disease of the arteries in which atheroma develops in the arterial wall. If the endothelium sustains damage low density lipoproteins enter the intima layer which are then taken up by macrophages. As the process continues lipid also accumulates outside the macrophages and the macrophages stimulate the production of collagen making the plaque more fibrous. This causes narrowing of the arteries, which in turn impedes blood flow to organs and tissues supplied by the affected artery. Usually atherosclerosis only becomes apparent when it produces symptoms. This occurs either when the blood flow through the

narrowed artery is unable to meet the demand of the tissues it supplies causing ischaemia, or when the atheromatous plaque ruptures (due to weakening of endothelial wall) exposing thrombogenic material beneath to the blood. This initiates platelet aggregation and the clotting cascade causing sudden occlusion of the artery or embolization of the clot to the distal arterial bed. The first of these processes causes clinical conditions such as angina (coronary arteries) or intermittent claudication (peripheral arteries) and the second process commonly causes myocardial infarction (coronary arteries), cerebral infarction (stroke) or acute limb ischaemia.

Figure 1.2: The continuum of atherosclerosis

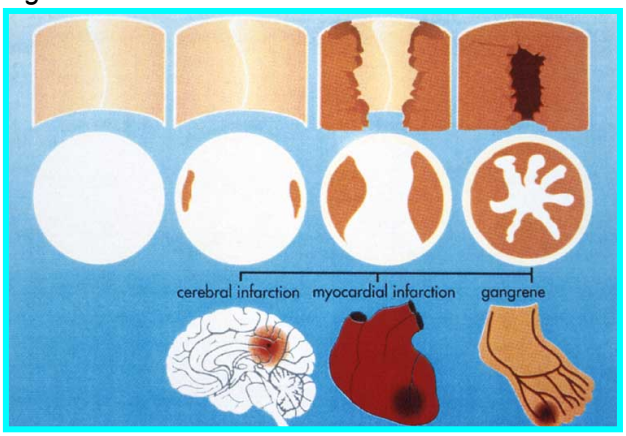


Illustration courtesy of JJF Belch.

The lesions take a number of years to develop (see figure 1.2) therefore subclinical atheroma will be present and developing insidiously in many people before they reach a stage where they produce clinically apparent disease. Atherosclerosis is a complex process involving inflammation and cellular proliferation in the arterial wall. Many epidemiological studies have demonstrated a number of risk factors that are associated with an increased risk of developing atherosclerosis and its clinical consequences (see table 1.1). Many of these are related to lifestyle in modern industrialised areas and include cigarette smoking, a high serum total cholesterol and low density lipoprotein, hypertension, and diabetes mellitus. Some risk factors are modifiable whereas others are not. The presence or absence of these risk factors is

used to estimate an individual's risk of developing cardiovascular disease (see section 1.2 below).

Table 1.1: Risk factors for developing cardiovascular disease

Risk Factor	**Association with cardiovascular risk**
Non-modifiable risk factors	
Age	Risk increases with age
Gender	Higher in males
Rheumatoid arthritis	Increased risk in those with rheumatoid arthritis.
Family history of CVD	Increased risk if there is a family history of CVD at a young age (less than 60) in one 1st degree or 2 or more 2nd degree relatives.
Ethnicity	Increased risk in some ethnic groups such as those of South Asian or African origin.
Apolipoprotein E (APOE) gene	Carrying at least one copy of e4 allele associated with increased risk. e2 allele associated with hyperlipoproteinaemia type III.
Modifiable risk factors	
Blood pressure	Hypertension associated with increased risk
Total cholesterol	Increased level associated with increased risk
Low density lipoprotein	Increased level associated with increased risk
High density lipoprotein	Low level associated with increased risk
Triglycerides	Increased level associated with increased risk
Tobacco smoking	Use is associated with increased risk. Increased smoking level is associated with increased risk. This includes passive smoking.
Social Deprivation	Living in an area of deprivation is associated with increased risk.
Diabetes mellitus	Increased risk in those with diabetes.
Diet	"Healthy" diet including more fruit and vegetables and less saturated fat and sugar associated with lower risk.
Exercise	Low levels of physical exercise associated with increased risk.
Obesity	Obesity associated with increased risk.
Alcohol intake	Low level intake (one or 2 units per day) associated with decreased risk but higher levels of intake associated with increased risk.
Chronic renal failure	Presence of chronic renal disease associated with increased risk.

1.1.3. Reducing risk of cardiovascular disease

A number of interventions, both lifestyle and medication based, have been shown to reduce the risk of developing atherosclerotic cardiovascular disease and mortality both in a primary and secondary prevention context. Guidelines have been produced describing the evidence base for a variety of interventions to reduce the risk of cardiovascular disease for both primary and secondary prevention, the latter including secondary prevention after coronary heart disease, stroke and peripheral arterial disease.[4-10] Lifestyle modification to reduce the prevalence of adverse behaviours such as smoking, diet, sedentary lifestyle and stress forms the cornerstone of cardiovascular risk reduction. Interventions that increase physical activity for example can lead to weight loss, lowered blood pressure, improved lipid profile and decreased insulin resistance. Detrimental behaviours are often seeded in childhood or adolescence but are maintained or even augmented by social environments. For this reason they are the target of public health measures. These aim to both alter the social environment and drivers of lifestyle choices and work in addition to advice and support aimed at individuals.

In addition to lifestyle and environmental interventions a number of medications have been shown to be effective in reducing CVD risk.

Statins

3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are known to reduce coronary events, a variety of coronary and cerebrovascular outcomes and mortality in those with known cardiovascular disease.[11-14] As a result their use has become an accepted and routine part of secondary prevention and is advised in a range of clinical guidelines for coronary artery disease, stroke and peripheral arterial disease.

Their benefit in primary prevention has also been demonstrated. A meta-analysis of the use of statins in primary prevention published in 2006 showed they reduce the risk of major coronary events, major cerebrovascular events, non-fatal myocardial infarction and revascularisations but not coronary heart disease death or all-cause death.[15] The relative risk reduction occurred whatever the baseline (low density lipoprotein) LDL level was and regardless of what risk factors were present and the relative risk reductions demonstrated were similar to those demonstrated in secondary prevention trials. The benefit in terms of absolute risk reduction was therefore greatest in those at highest risk of cardiovascular disease. Further trials were published following that review and a meta-analysis of trials of statins for primary prevention in people at low risk of cardiovascular disease (<20% in 10 years) demonstrated that statins brought about a statistically significant relative risk reduction for all-cause mortality (10% reduction), myocardial infarction, non-fatal myocardial infarction, stroke, unstable angina and revascularisation.[16] The effect on all-cause mortality, fatal or non-fatal myocardial infarction and stroke was similar for high and low potency statins. The baseline cholesterol level or change in lipid level during the trial did not modify the effects suggesting that statins have a benefit on relative risk reduction irrespective of the lipid profile. This may be due to anti-inflammatory effects of statins (that reduce the vessel wall inflammation which leads to atherosclerosis or instability of plaques that already exist), improved endothelial function and/or reduced thrombus formation. Other potential actions of statins include decreased oxidative stress, inhibition of myocardial hypertrophy, up regulation of endothelium derived nitric oxide, attenuation of P-selectin expression and leucocyte adhesion and mobilisation of endothelial progenitor cells all of which could have protective or healing qualities for CVD.[17] The benefit of statins at all levels of cardiovascular risk is reflected in recent guidelines from the National Institute for Health and Care Excellence (NICE) and the American College of Cardiology/American Heart Association which recommend offering treatment to those at lower risk than in previous guidelines.[6, 9]

A further meta-analysis of individual patient data from trials both looking at patients at low risk of cardiovascular disease and low risk patients from other trials but including some people with pre-existing cardiovascular disease (i.e. secondary prevention) demonstrated that statins reduced the risk of major vascular events by 21% per 1.0mmol/L LDL cholesterol.[18] The relative risk reduction was still observed in those estimated to be at very low risk of CVD (<5% 5 year risk) and in those with no history of cardiovascular disease.

A systematic review and meta-analysis of the use of statins for primary prevention from Cochrane demonstrated reductions in all-cause mortality (odds ratio (OR) 0.86, 95% CI 0.79 to 0.94), fatal coronary heart disease (CHD) events (risk ratio (RR) 0.82, 95% CI 0.70-0.96), non-fatal CHD events (RR 0.67, 95% CI 0.59-0.76), fatal (RR 0.83, 95% CI 0.72-0.96) and non-fatal (RR 0.77, 95% CI 0.62-0.96) CVD events, combined fatal and non-fatal stroke events (RR 0.78, 95% CI 0.68-0.89), combined fatal and non-fatal CHD, CVD and stroke events (RR 0.65, 95% CI 0.58-0.73) and revascularisations (RR 0.62, 95% CI 0.54-0.72).[19] One concern about the use of statins is that of adverse events and side effects. The Cochrane review of statins for primary prevention found that there was no significant increase in risk of all adverse events combined (cancer incidence, myalgia, rhabdomyolysis or haemorrhagic stroke) or in the number of trial participants stopping medication due to adverse events.[19] There was a slight increased risk of incidence of type 2 diabetes mellitus (RR 1.18, 95% CI 1.01-1.39) that was driven by the results of the JUPITER trial which used higher statin doses. The AFACPS/TexCAPS trial used lower doses of statins and showed no effect on diabetes incidence. There is no reliable data on quality of life in patients taking statins for primary prevention.

In summary the use of statins for primary prevention is efficacious in reducing the risk of a range of cardiovascular outcomes and death whatever an individual’s baseline risk is. However the biggest absolute risk reduction will be in those at highest baseline risk.

Their benefit needs to be balanced with the risk of adverse effects when deciding with individuals whether they wish to take them.

Antihypertensives

Many randomised controlled trials have demonstrated that blood pressure reduction with antihypertensive drugs in hypertensive people reduces morbidity and mortality from CVD. Therefore current UK guidelines from the British Hypertension Society and NICE[10] and from the Joint British Societies[20] recommend initiating antihypertensive treatment in those under 80 years old with stage 1 hypertension (clinic reading ≥ 140/90mmHg and ambulatory monitoring daytime average ≥135/85mmHg) and either target organ damage, established cardiovascular disease, renal disease, diabetes, or a 10-year CVD risk ≥20%, or in people of any age with stage 2 hypertension (clinic reading ≥160/100mmHg and ambulatory daytime average ≥150/95mmHg). This is more stringent than the recommendations in the European Cardiology Society guidelines.[4] Evidence suggests that treatment with antihypertensives is beneficial at all ages including those aged ≥80 years.[21] It has long been known that blood pressure lowering therapy in those with hypertension can reduce left ventricular hypertrophy[22, 23] and a meta-analysis has shown that beta-blockers induce less regression and angiotensin receptor blockers may induce larger regression than other classes of antihypertensives.[24] Regression of left ventricular mass during antihypertensive treatment is also independently associated with a better prognosis.[25]

Antiplatelet agents

A meta-analysis of use of aspirin for both primary and secondary prevention of vascular disease has been published.[26] As the focus of this thesis is on primary prevention I discuss only the use of aspirin in this context here. The review reported that in the primary prevention trials aspirin was associated with a reduction in serious vascular events (0.51% aspirin v 0.57% control per year, p=0.001) driven mainly by a

reduction in non-fatal myocardial infarction. There was no significant net effect on stroke (0.20% v 0.21% per year, p=0.4) or vascular mortality (0.19% v 0.19% per year, p=0.7). However aspirin allocation for primary prevention increased major gastro-intestinal and extracranial bleeds (0.10% v 0.07% per year, p<0.0001). Therefore the benefit of aspirin in primary prevention is uncertain as the reduction in CV events may be outweighed by increased haemorrhage.

1.2. Assessing cardiovascular risk

1.2.1. Background

The evidence for reducing risk of cardiovascular disease with statins and other therapies outlined above could imply that we should offer statins to the entire population. However this approach brings a number of economic and ethical questions.[27, 28]

Drugs cost money so more widespread use would lead to an increase in prescription costs despite the reducing cost of drugs to each individual as patents expire. However the economic effect is complex: if people live longer due to the preventive medication the lifetime cost per individual could increase as they will take medication for longer, and survival may be associated with older age with frailty, comorbidity and increased health and care costs compared to a sudden death from a myocardial infarction. Recent systematic reviews of the cost-effectiveness of the use of statins for primary prevention have attempted to address this complicated economic question. One review concluded that as statins become cheaper their cost-effectiveness increases and advocated more aggressive use of statins in primary prevention.[29] However this analysis used American healthcare costs which may not be generalizable to other countries with different healthcare systems. A second review concluded that the evidence on cost effectiveness is mixed and if other treatment options (such as

smoking cessation) are taken into account the cost-effectiveness is less positive.[30] Therefore with the changing costs of drugs it is currently not clear what the health economic impact would be of such a strategy in the United Kingdom healthcare system for example.

Even if such a strategy was cost effective this does not necessarily mean it is the right thing to do. A blanket or more widespread policy of statin use would involve exposing a large number of people to a drug that is going to bring them no personal benefit thus "medicalising" a significant proportion of the population who are in fact healthy. It has been estimated that the number needed to treat to prevent a single death from any cause among people at low risk of CVD would be 239 and to prevent a single non-fatal myocardial infarction would be 153.[16] Despite the apparent absence of increased risk of adverse events such as myalgia, rhabdomyolysis, cancer and haemorrhagic stroke with statins compared to control in the meta-analysis of use in primary prevention[19] any medication brings the potential for increased harm and interaction with other medications. Balances of benefits of risk from the meta-analysis are based on population averages and risks, which should be considered when advocating their use at the individual person level. Many people may not be prepared to be exposed to potential side effects if their individual probability of benefit is low: individual preference needs to be considered in decisions. The effect of lifelong statin therapy on quality of life is also not known. Others have argued[27] that identifying a larger population to start statin treatment may deflect attention from high risk groups where the absolute benefit is higher but where underuse of statins has been shown to be a problem.[31]

For these reasons there is an ongoing debate about whether statins should be offered more widely[28] and a number of guidelines have recently been updated and advise offering statin treatment more widely. Currently clinical guidelines from the Scottish intercollegiate guidelines network (SIGN)[5] and Europe[4] all recommend statins be prescribed for individuals predicted to be at high risk of developing disease (usually

defined as a 10 year risk ≥20%). However the recent update to the guidelines from the National Institute for Health and Care Excellence (NICE) advise offering statins to those with a predicted 10 year risk ≥10%[9] and those from the United States to those with a predicted 10-year risk of 7.5% or even 5%[6] reflecting the much debated lower threshold. A number of risk estimation methods are available to determine individuals' risk and decide on primary prevention in clinical practice. The derivation, role and limitations of these scores are discussed below.

1.2.2. Existing risk scores and charts

Results from observational studies have been used to generate a variety of predictive models that incorporate various markers of increased cardiovascular risk to estimate the absolute risk of developing clinically overt cardiovascular disease. Various cohorts of people from different backgrounds have been used to generate risk charts and scores to predict an individual's absolute risk of developing cardiovascular disease. Most of the earlier tools [32-36] used data from the Framingham cohort,[37, 38] while other groups have studied different populations to produce tools such as PROCAM[39], SCORE[40], ASSIGN[41], Seven Countries Study[42], QRISK[43] and CUORE.[44] However the different tools and scores are not directly comparable with each other. Some scores (such as some Framingham based tools, Seven Countries and PROCAM) use just cardiac disease as an outcome whereas others predict a wider range of cardiovascular disease. Some scores look just at mortality as an outcome whereas others also look at non-fatal events. Others have developed models looking purely at the outcome of stroke incidence.[45] Different groups have included different variables in their risk algorithms based on observed influence of different factors on the risk of cardiovascular disease to optimise their accuracy. Table 1.2 summarises commonly used risk scores/tools along with their end points and variables that are included.

Table 1.2: Summary of cardiovascular risk charts and scores

Scoring system	End points	Time (years)	Variables included
ASSIGN	• Death from cardiovascular causes • Coronary heart disease • Cerebrovascular disease • Coronary artery interventions	10	• Age • Sex • Family history of CHD/stroke • Diabetes • Rheumatoid arthritis • Smoking habit • Systolic BP • Total cholesterol • HDL cholesterol • Social deprivation
Framingham (1998)	• Acute myocardial infarction • Coronary heart death (sudden or not) • Angina pectoris • Heart failure	10	• Age • Systolic/diastolic BP • Total cholesterol • Diabetes • Smoking habit • HDL cholesterol • Antihypertensive treatment
PROCAM	• Non-fatal myocardial infarction • Fatal myocardial infarction • Sudden death	10	• Age • Systolic BP • LDL cholesterol • HDL cholesterol • Triglycerides • Smoking habit • Diabetes • Family history of MI • Angina pectoris
QRISK2	• Coronary heart disease • Stroke • Transient ischaemic attack	10	• Ethnicity • Age • Sex • Smoking status • Systolic BP • Total cholesterol:HDL ratio • BMI • Family history of CVD • Deprivation • Treated hypertension • Type 2 diabetes • Renal disease • Atrial fibrillation • Rheumatoid arthritis
Seven Countries Study (Italia)	• Coronary heart death • Fatal myocardial infarction • Non-fatal MI • Angina pectoris	10	• Age • Systolic BP • Total Cholesterol • Smoking habit (number of cigarettes)
SCORE	• Cardiovascular mortality • Ischaemic heart disease • Sudden death	10	• Systolic BP • Total cholesterol • Ratio total/HDL cholesterol • Smoking habit
CUORE	• Fatal/non-fatal major coronary events • Fatal/non-fatal major cerebrovascular events • Coronary and carotid revascularisation treatment • Sudden death	10	• Age • Systolic BP • Total cholesterol • Smoking habit • Diabetes

Clinical risk stratification models are measured in three domains: calibration, discrimination and reclassification. Calibration refers to how well a prediction model derived estimate of absolute risk agrees with the observed risk in a population. Discrimination refers to the ability of a model to distinguish between cases and non-cases. Reclassification refers to the ability of a model to correctly reclassify individuals into different risk categories and therefore whether a model will alter clinical decision making.

Evaluation of the various risk models in different population groups has found disparity between the predicted and observed event rates (i.e. calibration). In a representative British population the Framingham score gave a relative overestimation of 47% of death from coronary heart disease and 57% of a non-fatal coronary heart disease event.[46] Similar degrees of overestimation of risk were found in Augsberg and Munster in Germany.[47] Both the Framingham and PROCAM scores also overestimated the absolute risk in populations in France and Belfast in the PRIME cohorts[48] and in a Spanish non-diabetic population the Framingham and the SCORE systems over predicted the risk by 64% and 40% respectively.[49] A study of the predictive accuracy of the SCORE system in Austria found that it over predicted mortality in the group as a whole.[50] Interestingly a study of Framingham risk scores in socioeconomically deprived individuals found the converse of the studies described above; the score underestimated the observed incidence of disease by 31% in non-manual workers and 48% in manual workers.[51]

These observed discrepancies between predicted and actual events have led researchers to further adapt many of the tools to reflect the population group in which they are to be used.[52-55] For example different versions of the SCORE system have been devised to be used in areas with high and low incidence of cardiovascular disease by recalibrating the scores to reflect the underlying incidence of cardiovascular disease. In addition country specific versions for countries such as the Netherlands and

Belgium have been developed.[54, 56] Others have incorporated additional clinical and socioeconomic features to the traditional risk factors to improve predictive accuracy.[41, 43, 57, 58]

As might be expected with a large numbers of risk assessment tools available there are clinical implications in terms of decisions on whether to treat individuals. For reasons explained above this can vary greatly depending on which risk assessment method is used, which guidelines are followed or the underlying risk of cardiovascular disease in the area.[59-63] Despite refinements and recalibrations there are still limitations of these risk assessment tools in terms of their external validity and the tools cannot necessarily be directly transferred for use in populations from which they were not derived.

The difficulties in developing an accurate risk assessment tool reflect the complex nature of atherosclerotic disease. Relatively simple prediction tools can never expect to capture this complexity.

Firstly the risk scores look at the risk factor profile at a specific moment in time. Many of the factors however are dynamic and fluctuate over time so risk measured at these cross sections in time is likely to increase and decrease over a patient's lifetime. As atherosclerosis develops over a prolonged time period exposure to risk factors earlier in life may not necessarily be detected by "snapshot" risk assessment tools. Some studies have looked at the effect of treatment on changes to risk scores and have demonstrated that application of risk stratification and subsequent treatment of modifiable risk factors can reduce the mean risk estimation using the scoring methods described above.[64-66] However using this outcome measure may not necessarily always translate into a better clinical outcome because the disease process of atherosclerosis may have begun previously when the risk profile was less favourable.

The improved estimated risk may not be accurate after treatment because it will not reflect past vascular damage.

Secondly some individuals are more susceptible to environmental risk factors than others. This is likely to be due to genetic differences, differing inflammatory processes, differences in endothelial function, or other processes which can vary in the presence of the same environmental factors that are known to increase risk. This will lead to a degree of unpredictable distribution and behaviour of atherosclerotic plaques. As scores do not, and realistically never will, incorporate every individual factor that leads to cardiovascular disease we cannot expect them to accurately predict event rates even if they are recalibrated for different populations and levels of underlying disease.

Calibration is only part of the accuracy of a score. Their main use as advocated in guidelines[4, 5, 9] is that of discrimination between future cases and non-cases to determine who should be prioritised for preventive treatment. It has been argued that discrimination is the more important function of the scores rather than absolute risk prediction.[67] A number of studies looking at the discriminatory ability of a variety of scores applied to an English and Welsh population found that they all had similar ability as assessed by area under the receiver operating characteristic ROC curve analysis (c-statistics ranged from 0.740 to 0.792).[68, 69] The nature of the risk scores as described previously means that they will not be 100% sensitive or specific and a trade-off has to be reached when selecting what is classified as high risk. Many people who are assessed as being “low” risk go onto develop or die from myocardial infarctions, strokes or peripheral arterial disease as although their risk is lower the group is more numerous. Conversely many who are assessed as being “high” risk never develop such diseases even though their risk is higher. One could argue they are therefore taking primary preventive medication without any benefit but with all the potential risks of side effects and expense. The threshold for treating could be reduced which would increase the sensitivity of the test to those who will have events but at the

expense of specificity as we treat more people who will not develop disease. Only by increasing then area under the ROC curve by improving the risk estimation itself will risk discrimination be improved.

The presence of events in those assessed as low risk by risk estimation tools is supported by evidence that such individuals have evidence of atherosclerotic disease that puts them at increased risk of cardiovascular disease.[70-72] The extent of plaque progression is associated with increased estimated risk of clinical events as assessed by Framingham, PROCAM and SCORE algorithms.[73] It could therefore be argued effectively that if individuals have evidence of subclinical vascular damage they may benefit from primary preventative medication and treatment, which they are currently denied by current guidelines which use risk estimation alone without assessing for subclinical disease.

These shortcomings maybe one reason why the use of the tools in clinical practice is low in a variety of European, North American and South American settings.[74-78] Lack of time, perception that scores oversimplify risk or lead to medication overuse and poor patient compliance are also quoted as being reasons for the low level of use.[79] Some have suggested that a simple measure of waist circumference rather than use of a risk scoring tool may be a quicker screening tool for those with higher cardiovascular risk who merit further work-up.[80] Therefore despite the presence of tools, and evidence based treatment guidelines for primary prevention cardiovascular risk remains high.[81]

A range of biomarkers to either improve or enhance risk stratification models that use “traditional” risk factors or screen for asymptomatic cardiovascular disease have been investigated. The aim is to improve calibration or discrimination of risk scores. Biomarkers investigated include blood tests, imaging techniques and physiological

examinations. The potential new biomarkers relate either to susceptibility to vascular damage, inflammation or evidence of end organ damage.

1.2.3. B-type natriuretic peptide (BNP)

B-type natriuretic peptide (BNP) is a hormone that regulates loss of water (diuresis) and sodium (natriuresis) by the kidneys. It belongs to a family of peptides that also includes atrial (A-type) natriuretic peptide (ANP). BNP is co-expressed with ANP in secretory vesicles and its secretion is increased in response to pressure and volume overload in the atria and ventricles.[82] BNP is produced initially as pre-prohormone BNP before being processed to proBNP. This is then cleaved to the biologically active BNP and the non-biologically inactive N-terminal proBNP (NT-proBNP).[83] Both of these substances can be detected in the bloodstream and assays are available to quantify them. A large number of studies have been performed using both these markers and their association with cardiovascular disease and physiology. However BNP and NT-proBNP have different half lives so they are not directly interchangeable. The following discussion includes studies of both BNP and NT-proBNP and specifies which marker was studied in each case.

The use of BNP or NT-proBNP in the diagnosis of heart failure has become well established and is now included in the NICE[84] and SIGN[85] guidelines on the subject. However BNP or NT-proBNP may have a role in detecting poor cardiovascular health or pre-clinical disease, and predicting cardiovascular disease and death in patients without heart failure, both with and without pre-existing CVD and whether or not they have cardiovascular risk markers.[86]

BNP and vascular abnormalities and function

Elevated levels of BNP and NT-proBNP have been linked with various abnormalities of vascular function which in turn have been associated with overt clinical cardiovascular

disease. A few studies have reported an association between elevated natriuretic peptides and markers of vascular stiffness. One studied BNP levels in patients with type 2 diabetes but no evidence of frank left ventricular dysfunction.[87] The researchers found that an increased augmentation index reflecting aortic stiffness is an independent predictor of BNP level even when the BNP level is within the “normal” range. This is supported by the findings of a study of hypertensive patients which found that higher plasma NT-proBNP tertiles were associated with a variety of markers of impaired aortic elasticity (larger systolic and diastolic aorta diameters, longer deceleration time of E wave velocity and isovolumic relaxation time).[88] This study also found that NT-proBNP levels were higher in the hypertensive subjects than normotensive controls supporting the idea that levels may reflect cardiovascular stress. Even in “healthy” men stiffening of arteries, as measured by pulse wave velocity and pulse pressure, is significantly correlated with BNP levels.[89] Further evidence of an association with impaired endovascular function is provided by a study that demonstrates that BNP is independently related to endothelium-dependent vasodilatation as assessed by an invasive acetylcholine induced forearm vasodilation technique.[90] The study included both patients with and without cardiovascular risk factors.

In a study of patients with rheumatoid arthritis but no clinical coronary artery disease, hypertension, diabetes or advanced chronic kidney disease elevated NT-proBNP levels were associated with increased carotid intima media thickness (C-IMT) which indicates subclinical atherosclerotic disease.[91] In a large study (n=2445) of patients without heart failure or renal insufficiency higher log NT-proBNP were independently associated with higher coronary artery calcium scores derived from electron beam computed tomography (CT) scans.[92] This association remained when patients with low left ventricular (LV) ejection fractions, LV hypertrophy, angina or previous myocardial infarction were excluded. A study of patients with peripheral arterial disease

found that NT-proBNP levels are 2.5 fold higher in those with poorly compressible (i.e. calcified) peripheral arteries.[93]

BNP and subclinical arterial disease

Log NT-proBNP has been shown to be an independent predictor of the presence of silent myocardial ischemia (stenosis of >50% detected by angiography) in patients with diabetes.[94] The authors reported a high negative predictive value for NT-proBNP (94.3%) however this study was only small (n=40). A larger study of high risk diabetic patients without heart failure reported that an NT-proBNP ≥38pg/ml was a significant predictor of silent coronary artery disease (CAD) detected using stress myocardial scintigraphy and subsequent angiography.[95] A meta-analysis of studies investigating the association of BNP with inducible myocardial ischaemia found that an increased BNP level can identify inducible ischaemia with an AUROC of 0.71.[96] This meta-analysis included populations with suspected or known coronary artery disease in addition to those without disease however a study of patients with type 2 diabetes found that BNP was an independent predictor of an abnormal exercise tolerance test even in a subgroup with no history of ischaemic heart disease or heart failure.[97] The use of exercise induced changes in BNP may also be helpful detecting CAD. In a study of patients referred with chest pain and LV ejection fraction >50% and no previous history of CAD a 1.3 fold increase in BNP after exercise (Bruce protocol exercise tolerance test) was associated with an 11 times greater odds of having angiographically proven CAD.[98] This threshold produced a sensitivity of 81.8% and specificity of 71.8%. The presence of silent myocardial infarctions (MI) detected by delayed-enhancement magnetic resonance imaging (DE-MRI) is associated with higher levels of NT-proBNP than in those who had no evidence or history of MI.[99] A study of asymptomatic patients with type 2 diabetes found that NT-proBNP was associated with the presence of coronary, carotid or peripheral atherosclerosis but this association did not persist when the data was adjusted for conventional cardiac risk factors.[100]

BNP and cardiac function and structure

BNP levels correlate with increased left ventricular mass and subtly lower left ventricular ejection fraction in those with no clinical evidence of heart failure.[87] This is supported by the findings of another study of patients with preserved systolic function which showed that more severe left ventricular hypertrophy and impaired diastolic function were independent predictors of higher BNP.[101]

BNP and cardiovascular events and mortality

Associations between BNP/NT-proBNP levels and a variety of clinical outcomes have been reported. Increased NT-proBNP[102, 103] and BNP [103, 104] levels are associated with increased cardiovascular mortality, heart failure and stroke in patients with stable CAD. Elevated levels of NT-proBNP are also independently associated with the risk of stroke in patients with atrial fibrillation (AF)[105] and NT-proBNP and BNP levels can predict cardiovascular events following vascular surgery.[106] In patients who have had a stroke but have no clinical evidence of previous cardiac ischaemia NT-proBNP independently predicts future MI[107] and BNP correlates with reversible cardiac ischaemia.[108]

In population studies of patients unselected on the basis of the presence or absence of pre-existing CVD increased levels of NT-proBNP have been associated with higher rates of all-cause mortality, cardiovascular events, coronary events and incidence of AF.[109-115] A higher level of BNP is associated with CV events, cardiovascular mortality, all-cause mortality, heart failure, stroke and AF but not CHD events in a similar population.[116] An evaluation of BNP as part of a bank of other biomarkers in the Framingham Heart study found that BNP predicted the risk of death and first cardiovascular event however the use of the bank of biomarkers only added moderately to the prediction of risk in individuals.[117] In a population of patients with diabetes (and mixed history of absence/presence of CVD) NT-proBNP <125pg/mL has

been shown to have a good negative predictive value for CV events within 12 months.[118]

A systematic review and meta-analysis of prospective studies examining the association of BNP and NT-proBNP with CVD reported that after adjustment for conventional risk factors the relative risk of CV events in those in the highest tertile of BNP or NT-proBNP compared with those in the lowest tertile was 2.68 (95% CI, 2.07-3.47) for general populations.[86] Increased NT-proBNP is associated with increased 5 year risk of stroke (both ischaemic stroke and intracerebral haemorrhage) in a population with no prior evidence of cerebrovascular disease.[119] The association of NT-proBNP with new onset heart failure and CV death has been demonstrated in those aged 70 and over[120] and it may be that the association of NT-proBNP with CV endpoints increases with age but may not be significant in younger age groups.[121]

The association between natriuretic peptides and other vascular diseases has also been studied. Elevated NT-proBNP is associated with poorer cognitive performance in community dwelling older adults.[122] The development of dementia and the decline in Mini Mental State Examination (MMSE) also appear to be associated with elevated BNP which remains significant when corrected for baseline MMSE.[123] In those with known cerebrovascular disease an independent relationship between log transformed BNP levels and dementia severity as measured using the Dementia Rating Scale has been demonstrated.[124] In a small case control study BNP levels were found to be significantly higher in patients with subcortical vascular dementia than in those with Alzheimer's dementia and healthy controls.[125] However it is not clear if the results were adjusted for vascular risk factors so the higher levels of BNP may reflect the higher vascular risk factor burden in those with vascular dementia rather than the presence of vascular dementia itself. An association between increased NT-proBNP and incident disability in older adults has been described.[126]

However is the prognostic ability described above also demonstrable in populations with no pre-existing evidence of CVD? A number of studies of asymptomatic populations have demonstrated that BNP[127-130] and NT-proBNP[127, 131, 132] predict mortality and CV events. The hazard ratios for death range from 1.3 to 5.7 and those for cardiovascular events range from 1.3 to 13.8. For both outcomes the larger studies quote figures that are lower suggesting the association may only be slight. It is unclear whether the association with BNP is continuous or whether there is a threshold effect as different studies have used different cut offs and methods.

A study of healthy normal people defined as the absence of traditional clinical CV risk factors and no echocardiographic structural cardiac abnormalities found that NT-proBNP was not predictive of either death or CV events.[133] This may suggest that in a truly low risk population NT-proBNP may not be useful for further risk stratification. However the same study found that NT-proBNP levels above age and sex specific 80th percentiles were associated with increased risk of death, heart failure, stroke, and MI after adjustment for clinical risk factors and structural cardiac abnormalities in a population free of symptomatic heart failure but with either CV risk factors or impaired cardiac function demonstrated on echocardiogram. A greater proportion of this population had an NT-proBNP level greater than their age and sex specific 80th percentile than the healthy population. Therefore even in a population who may appear to be healthy it is possible that higher natriuretic peptide levels may help recognise those with a subclinical CVD.

BNP and traditional cardiovascular risk factors

The correlation of natriuretic peptide levels with existing risk estimation tools has also been evaluated. In patients with type 2 diabetes but no pre-existing coronary artery disease or stroke log BNP level correlates with the 10-year risk for CHD and stroke as assessed with the Framingham risk score.[134] BNP levels are also significantly higher in those with a high cardiovascular risk as assessed by the New Zealand Risk

Score.[134] There is evidence to support this correlation in a general (not exclusively diabetic) population. In one study ROC analysis showed the area under the curve was comparable to that for the Framingham Risk Score when cut offs for BNP of 37pg/ml and 55pg/ml were used in men and women respectively.[135] A further comparison of existing risk scores and natriuretic peptides found that NT-proBNP correlated less with Framingham Risk Score and SCORE risk estimation algorithms than the alternative NT-proANP.[136] However no actual cardiovascular endpoints were measured so it is not possible to say whether the NT-proBNP or existing clinical risk scores were more effective at predicting actual events.

In patients with established cardiovascular disease (i.e. secondary prevention) the addition of NT-proBNP levels to clinical assessment of traditional cardiovascular risk factors and or echocardiographic parameters appears to improve prediction of future cardiovascular events and cardiovascular death.[137, 138] However the use of risk factor modification and secondary preventative medication is already known to be beneficial in this population so the additional prognostic information provided by NT-proBNP has limited clinical usefulness (i.e. has limited reclassification use).

Importantly many studies have found that BNP[139-141] and NT-proBNP[92, 140] levels are significantly higher in women compared to men. The reasons for the difference in BNP level have been investigated in a population free from cardiovascular disease or cardiovascular medication in who LV failure had been excluded by echocardiogram.[139] The higher levels were not explained by gender related differences in blood pressure, renal function or cardiac structure but may be related to oestrogen status. As a higher level is seen in women who have a lower cardiovascular risk than men gender specific references ranges are likely to be needed for each gender.

Incremental benefit of adding BNP

Large prospective studies have found that adding NT-proBNP levels to a Framingham Risk Score based model improves the accuracy of risk predictions[142-144] and can result in a net reclassification improvement of between 8.2% and 13.3%[143, 144] in a population of asymptomatic individuals (i.e. primary prevention). This effect persists in those older than 55 years of age.[144] Further evidence of a possible supplementary role of natriuretic peptides is provided by studies that used BNP[117, 145, 146] or NT-proBNP[117, 146, 147] markers in combination with other biomarkers to improve the accuracy of event prediction however the effect of the addition of biomarkers is often only small. A systematic review reported the effect of the addition of BNP or NT-proBNP to risk models on their discriminatory ability: improvements in area under the ROC curve were only small in the studies looking at general populations (increases in the c statistic range 0.007-0.03).[86] Also not all studies of the ability to improve event prediction are positive. A case control study found that the addition of NT-proBNP to a Framingham Risk Model did not improve calibration of a prediction model or result in reclassification of individuals' risk.[148] A smaller study of patients with rheumatoid arthritis but no cardiovascular disease did not demonstrate an improvement over Framingham Risk Score alone when NT-proBNP was added.[149] One other large prospective study reported that incorporation of NT-proBNP into a risk prediction model did not significantly improve c statistics of the model.[150] It is unclear which model was used in this study so direct comparison with models in use in clinical practice is difficult.

What is the role of BNP?

BNP or NT-proBNP are associated with impaired vascular function, calcification, presence of subclinical disease, and increased estimated and actual cardiovascular risk in a variety of populations. Although evidence about their ability to improve calibration, discrimination or reclassification beyond traditional risk factor models is mixed, possibly due in part to heterogeneity in study design particularly in identifying

the study population, it appears that BNP/NT-proBNP levels reflect an increase of stress on the cardiovascular system and they are likely to be a common end point for a number of cardiovascular abnormalities. It therefore follows that an elevated BNP level could conceivably be used to screen for atherosclerotic disease or target organ disease that requires further characterisation and phenotyping.

In a study examining the usefulness of natriuretic peptides for screening for increased left ventricular mass and left ventricular systolic dysfunction in a community based study as part of the Framingham Study BNP the area under the curve (AUC) was at or below 0.75 for increased LV mass and LV systolic dysfunction (except moderate to severe systolic dysfunction).[151] This was true when all participants, participants aged 60 years or older, those with hypertension, those with prevalent cardiovascular disease and those with 2 or more high risk features were analysed separately. The authors suggested that the use of BNP for detection of elevated LV mass and left ventricular systolic dysfunction was suboptimal and therefore of limited usefulness as a mass screening tool. However a study of people receiving primary prevention for cardiovascular risk factors found that the BNP was able to more accurately predict cardiac target organ damage (left ventricular hypertrophy, left ventricular diastolic dysfunction, left atrial enlargement, left ventricular systolic dysfunction or cardiac ischaemia).[152] The AUC for BNP (0.78) was similar to other screening tests used clinically such as prostatic specific antigen (PSA) for prostate cancer (AUC 0.68-0.78)[153, 154] and mammography for breast cancer (AUC 0.78).[155] BNP performed better than high sensitivity troponin T, microalbuminurea, estimated glomerular filtration rate, uric acid and abnormalities on a 12 lead ECG. It therefore appears that BNP may have a role in screening for a range of abnormalities but then require follow up with further evaluation to determine the nature of any abnormality in each individual.

1.2.4. Other candidate tests

Other tests have been investigated to see if they add any additional predictive ability to identify those at risk of CVD. C-reactive protein (CRP) has attracted a great deal of research attention as a marker of inflammation that plays a key part in formation of atherosclerosis. This has been furthered with the emergence of high sensitivity assays.[156, 157] CRP is an independent predictor of death.[117] High sensitivity CRP (hsCRP) has been shown to correlate with the calculated 10 year Framingham Coronary Heart Disease risk in men and women.[158] The results of this study could reflect hsCRP being a marker of vascular risk however others have shown hsCRP to be an independent predictor of future myocardial infarction and ischaemic stroke.[159] The Reynolds risk score was developed by adding hsCRP and parenteral history of MI before the age of 60 years to the usual risk factors used in the Framingham score.[160] This score was reported to be more accurate in predicting cardiovascular disease when compared to the Framingham Risk Score particularly where people are classed as being at “intermediate risk”.[160, 161] Using cut offs of levels of hsCRP of <1.0mg/l, 1.0-3.0mg/l and >3.0mg/l to reflect low intermediate and high risk respectively, predicted risk in those previously assessed to be at intermediate risk as calculated by Framingham Risk Score was adjusted in 66% of patients.[162] However there may be limitations to the use of hsCRP. The number of intermediate risk individuals reclassified as high risk when using hsCRP depends on the cut off level used and the demographics of the individuals being screened.[163] In this way the limitations are similar to those of the original risk stratification models.

Soluble P-selectin was shown to be positively and independently associated with Framingham Risk Score and presence of atherosclerotic plaques.[164] Non-high-density lipoprotein cholesterol was found in one study to be more strongly associated with subclinical atherosclerosis, as measured by coronary artery calcification, than conventional lipid values.[165] Receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) has been suggested as a possible marker of

vascular vulnerability.[166] Homocysteine and renin levels have also been shown to predict death and urinary albumin to creatinine ratio predicted death and first major cardiovascular events although their use in a panel of biomarkers only moderately improved prediction above the use of traditional risk factors.[117]

The level of troponin T detected using a highly sensitive assay (hsTnT) in a population based cohort was associated with left ventricular hypertrophy, left ventricular systolic dysfunction and all-cause mortality.[167] The troponin T level remained independently associated with mortality when adjusted for traditional cardiovascular risk factors, CRP, chronic kidney disease and NT-proBNP. HsTnT levels are also associated with cardiovascular risk as estimated by Framingham Risk Score.[168] Increasing hsTnT levels on serial measurements have also been shown to be associated with cardiovascular events.[169] As discussed previously in a population receiving treatment for primary prevention of cardiovascular disease hsTnT was an independent predictor of cardiac target organ damage when corrected for age, sex, and estimated glomerular filtration rate.[152] However it did not perform as well as BNP. The use of a supersensivity troponin I assay led to an improvement in net reclassification for major adverse cardiac events in people at intermediate risk.[170] In the Framingham study the addition of a biomarker panel including high sensitivity troponin I improved prediction (improved c statistic and net reclassification improvement over using standard risk factors).[171]

Some have used exercise tests to improve risk estimation or detect subclinical atherosclerosis. A positive exercise tolerance test (defined as ST-segment depression during or following exercise) when added to conventional risk factors improved the positive predictive value in one cohort study.[172]

A series of systematic reviews published in 2009 investigated the ability of a range of biomarkers and tests to successfully reclassify those at intermediate risk of CVD as

assessed by Framingham Risk Scores.[173] Based on these results available at that time it was advised that the evidence for using CRP, lipoprotein, homocysteine, leukocyte count, fasting glucose concentration, presence of periodontal disease and ankle brachial index was insufficient to recommend their use in assessment of CHD risk. This review did not include any studies on high sensitivity troponin and I found no published reviews of troponin in healthy populations to date.

1.2.5. Imaging to predict cardiovascular disease

The evidence suggests that BNP is able to identify those who have subclinical silent cardiovascular disease. However, as with most screening tests, the test is not 100% specific and therefore further characterisation or phenotyping of any underlying abnormality is desirable. A variety of imaging techniques including echocardiography, CT, nuclear medicine perfusion scanning, ultrasonography and magnetic resonance imaging have been developed which can be used to detect abnormalities which in turn have been associated with clinical outcomes. As this study used MRI this modality is reviewed in most detail below.

Magnetic resonance cardiac imaging

The development and improvement in magnetic resonance imaging has allowed the modality to be used to assess cardiac mass, function and detect cardiac disease. A few large epidemiological cohorts and some smaller studies have used MRI to assess left ventricular mass (LVM) or other cardiac parameters. These have allowed characterisation of “normal” MRI derived parameters and have shown associations with a variety of risk factors and cardiovascular outcomes.[174-178]

The Multi-Ethnic Study of Atherosclerosis (MESA) recruited 6500 men and women aged 45-84 years and free from established cardiovascular disease from different ethnic backgrounds in the United States.[174] Participants underwent cardiac MRI imaging to determine LVM and LV function as well as coronary calcium assessment

using CT, measurement of brachial artery endothelial dilatation, C-IMT and carotid artery distensibility using ultrasound, ankle-brachial blood pressure index in addition to “traditional” cardiovascular risk factors, socioeconomic, lifestyle factors and psychosocial factors. Participants have been followed up for CV events and mortality. The aims of the study included to determine characteristics that relate to progression of subclinical disease to clinical CVD and determine the incremental value above traditional risk factors of new factors in predicting CVD.

The Dallas Heart study imaged almost 3000 participants using thoracic MRI to measure LVM, LV function and aortic distensibility.[175] The study population was aimed to represent the population of the United States so recruited people from various ethnic backgrounds. It did not exclude people with established or increased risk of cardiovascular disease. It aims to produce population estimates of biological and social variables that identify ethnic differences in cardiovascular health and produce hypotheses on underlying mechanisms for these differences.

1794 participants of the Framingham Heart Study Offspring cohort have undergone LV short-axis orientated contiguous multislice MR of the left ventricle. A healthy subgroup of 852 participants free from clinical cardiac disease, hypertension and treatment for hypertension have been studied to produce normal LV parameters for this population.[177]

Cardiac parameters appear to be different in men and women and in different ethnic groups. LVM derived from MRI has consistently been shown to be lower in women compared to men.[177, 179-183] The Dallas Heart study found that African Americans have increased LVM compared with White-Americans even when adjusted for fat mass, fat-free mass, systolic blood pressure, age, gender and markers of socioeconomic status.[184] However African Americans do not have a higher prevalence of reduced left ventricular ejection fraction (LVEF).[180] Another analysis

from the Dallas Heart study found that LVEF was higher in women compared to men secondary to a higher stroke volume when adjusted for end diastolic volume and other potential confounders.[185] A subpopulation of the MESA study excluding smokers, those with hypertension (>140/90mmhg), increased fasting glucose, increased cholesterol and decreased HDL was investigated to determine normal MRI derived cardiovascular values by age, sex and ethnicity.[182] LV volumes except end systolic volume were inversely associated with age in both sexes. LVM indexed for body surface area was not associated with age for either sex (although unindexed LVM was in men). LVM was largest in African Americans and smallest in Asian Americans. A similar study of a subpopulation of the Framingham Heart study offspring cohort free of hypertension or cardiovascular disease found LV volume measures corrected for body surface area were greater in men compared to women but there were no differences in LVEF.[183]

Cardiac MRI parameters are associated with CV risk and outcomes. In those aged 30-50 years old concentric left ventricular hypertrophy (LVH) was associated with a high lifetime predicted risk of CVD even in those without detectable coronary artery calcium in the Dallas heart study.[186] In a multivariable linear regression analysis the MESA study demonstrated an association of higher systolic blood pressure and body mass index (BMI) with larger LVM and LV volumes after correction for socioeconomic variables and height.[187] Current smoking and diabetes were also associated with a greater LVM and lower stroke volume and ejection fraction. Increased LVM indexed for fat free mass was associated with subclinical atherosclerosis (detected by coronary artery calcification).[188] However LVM has also been associated with a high ankle-brachial pressure index (indicating stiff arteries) which persisted after correction for measures of atherosclerosis in the coronary and carotid arteries (assessed using coronary artery calcification and carotid intimal media thickness respectively)[189] suggesting that increased LVM may not be entirely caused by detectable sub-clinical atherosclerosis. LVM was associated with endothelial dysfunction assessed by brachial

flow mediated dilation independent of age, gender, race, systolic BP, diabetes, smoking, weight, statin use, HDL and LDL.[190]

These associations between markers of vascular health and predicted risk also translate into clinical outcomes. Increased LV mass to LV end diastolic volume ratio (a marker of concentric ventricular remodelling) was positively associated with incident coronary heart disease and stroke in a Cox proportional hazard model as part of the MESA study.[191] This association persisted after adjustment for baseline cardiovascular risk factors (age, sex, ethnicity, diabetes, cigarette smoking, total cholesterol, HDL, use of antihypertensive or lipid lowering medication and systolic and diastolic blood pressure). LVM and LVM/volume ratio were also associated with the combined endpoint of coronary artery disease, stroke and heart failure when adjusted for traditional risk factors.[181] The same study found that risk prediction for heart failure was improved significantly by adding LVM to traditional risk factors.

Beyond left ventricular mass and volume assessment the use of delayed myocardial enhancement to detect myocardial infarction has been evaluated. The Age, Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) Study used gadolinium enhanced cardiac MRI in a subset of 1000 participants to look for myocardial infarction and determine cardiac output and assess wall motion.[176] This study population was drawn from an established population study cohort of people who were born between 1907 and 1935 and thus has an older population than some other studies. It included people with existing cardiovascular disease. It is aiming to comprehensively study ageing by assessing a range of phenotypic variables and relate these to earlier life risk factor assessments and genetic information. Presence of clinically unrecognised MI detected by contrast enhanced cardiac MRI was associated with increased mortality when adjusted for age, sex, diabetes and recognised MI (from ECG).[192] This supports evidence from a smaller study of patients with diabetes which found late gadolinium enhancement detected MIs in those with no previous clinical diagnosis of

MI was associated with increased rate of cardiac events and death.[193] In a sub-study of participants of the PIVUS study not all late-enhancement detected MIs were associated with atheroma detected by MRI angiography or carotid ultrasound, or with cardiovascular risk factors.[194] The authors suggested that this could be because unrecognised MIs either have a non-atheromatous aetiology or they manifest at an earlier stage of disease. These findings suggest a possible incremental benefit of identifying subclinical infarcts as part of a screening process.

Magnetic Resonance Angiography (MRA)

Atheroma develops over a period of time and is likely to be present subclinically for some time before clinical disease becomes apparent potentially offering a window to intervene to prevent clinical disease. This is supported by evidence from the Framingham Offspring study where T2 weighted black-blood thoracoabdominal aortic imaging found evidence of atheroma in 38% and 41% of women and men respectively free of cardiovascular disease.[195] The presence of plaque correlated with the Framingham coronary risk score for all women and for men after adjustment for age. Mean aortic wall thickness of the abdominal aorta was associated with an increased risk of cardiovascular events and increasing aortic plaque burden was associated with an increased risk of non-fatal non-cardiac vascular events in the Dallas Heart Study.[196]

Recently there has been a growing interest in and development of the technique for whole body contrast enhanced MRI angiography (WB CE-MRA).[197-203] As scanners have improved and scanning protocols have evolved the time required for scans (often combined with cardiac or other solid organ imaging) has reduced. WB CE-MRA has shown to have a good sensitivity and specificity for significant stenosis when compared to digital subtraction angiography albeit in populations with peripheral arterial disease.[201, 204, 205] In a population free from clinical disease a validation study found that findings of arterial stenosis or previous MI agreed with findings from other

tests (Doppler ultrasound for peripheral arteries and cardiac angioplasty, ECG, stress testing or echocardiography for cardiac disease including previous MIs).[198]

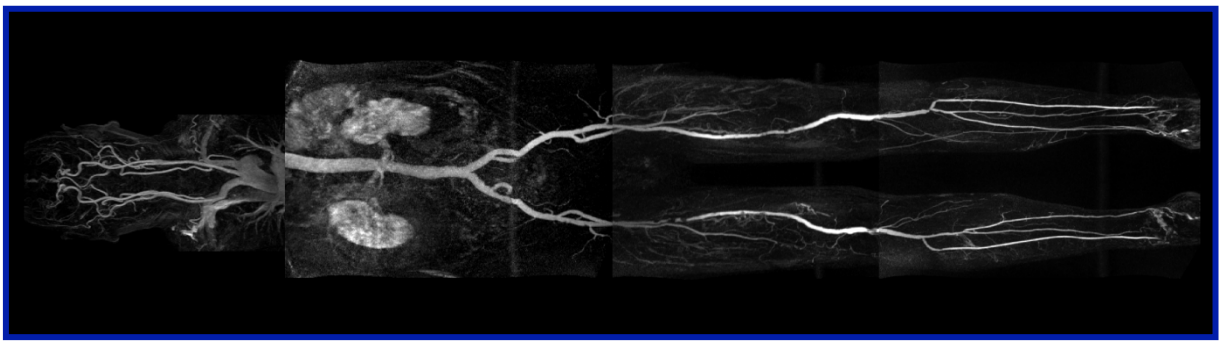
In addition to the diagnostic accuracy of the technique patient acceptance of WB CE-MRA is important especially if it is to be used as a screening tool. A prospective study of patients with peripheral arterial disease who underwent both WB CE-MRA and digital subtraction angiography found that WB CE-MRA was the preferred technique.[206]

Various groups have developed a variety of slightly different scoring systems to quantify whole body atheroma burden by quantifying luminal narrowing.[207-209] These scores have been correlated with various cardiovascular risk factors and presence of disease in other vascular beds. In a study of 50 people suspected of having coronary artery disease but no history of extra-cardiac atherosclerosis those with significant coronary artery disease shown on coronary angiography had a higher atheroma burden on MRA.[209] The same study also found the whole body atheroma burden was associated with predicted coronary risk using both the PROCAM and Framingham Risk Scores.

A subpopulation of 306 70 year olds from the PIVUS study cohort in Sweden, some of whom had a history of cardiovascular disease, underwent a WB CE-MRA using gadodiamide contrast which was used to give a total atheroma score. This score was associated with traditional cardiovascular risk factors (male sex, systolic blood pressure, cigarette pack years and HDL) as well as the Framingham Risk Score.[208] Even in those without evident CVD 26% had significant vascular abnormalities.[210] Importantly prospective follow up of the cohort found that the total atheroma score was associated with the combined end point of cardiac death, MI, stroke or coronary revascularisation when adjusted for multiple risk factors and improved discrimination and reclassification when added to the Framingham Risk Score.[211]

A WB CE-MRA derived atheroma score was also associated with predicted 10 year risk for CHD, fatal CHD and stroke and was significantly higher in those with features of metabolic syndrome in patients with longstanding diabetes.[207]

Figure 1.3: Whole body magnetic resonance angiogram



Courtesy of Prof Jill JF Belch and Prof J Graeme Houston

Other imaging techniques

Other imaging modalities and techniques have also been evaluated. Coronary artery calcification can be determined by electron beam CT. This has been described as both a marker of susceptibility to vascular damage and as a marker of subclinical damage. A meta-analysis of 4 cohort studies found that a coronary artery calcium score derived by electron beam CT in asymptomatic individuals is an independent predictor of CHD events.[212] This is the case in both younger (aged <40 years) [213] and older patients[213, 214] with no baseline coronary heart disease risk factors. Coronary artery calcification improves prediction of coronary events[214, 215] and this may be particularly useful in those with intermediate risk in whom it can be difficult to decide on the need for treatment.[216] It is also an independent predictor of all-cause mortality and can improve prediction of this end point.[217, 218]. A study of combined CT and PET using 18F-sodium fluoride (18F-NaF) showed that the technique was able to identify and localise ruptured and high risk coronary artery plaques.[219] Although this study was performed in a population of people with myocardial infarction or stable

angina it is conceivable that the methodology could be used to detect preclinical disease in an asymptomatic population. The risk derived from exposure to ionising radiation, however, needs to be considered if using CT as a screening tool. For this reason MRI may be more acceptable.

Exercise thallium perfusion scans in healthy siblings of individuals with young onset coronary heart disease was shown to be helpful in predicting future cardiac events[220] and has been shown to identify subclinical atherosclerosis in such high risk individuals.[221]

Evidence of vascular disease has been detected by increased carotid intima-media thickness (C-IMT) in those with a low Framingham Risk Score.[222] Framingham based risk prediction of coronary events has been improved by adding C-IMT in a number of studies[172, 223-225] although its role in predicting stroke is less clear.[226] A meta-analysis of common C-IMT thickness measurements in cardiovascular risk prediction concluded that the addition of the measurement to Framingham Risk Score improved the 10 year risk prediction of first time MI or stroke but only by a small amount.[227] The c statistic for predictive models with and without C-IMT were similar but there was a net classification improvement of 0.8% (95% CI 0.1-1.6%) with the addition of C-IMT. This was slightly better for those at intermediate risk (3.6%, 95% CI 2.7-4.6%) however this small improvement is unlikely to be of clinical importance.

1.3. Summary – is the future screening rather than risk estimation?

In summary, there is a desire to improve how we assess individuals' risk of developing cardiovascular disease to allow targeting of primary preventative measures including costly and potentially side effect inducing medication to those most likely to benefit. Current risk prediction tools based on observational population data are limited in their ability to accurately predict risk at the individual level. Therefore many individuals either do not receive medication from which they could benefit or receive medication that has

no benefit. This makes it difficult to give accurate information to individual patients (rather than at a population level) about the benefits of interventions such as statins and allow them to make an informed decision. A number of novel biomarkers have been studied to improve risk prediction. Many of these have shown varying success possibly reflecting the complex interaction of factors that lead to atherosclerotic disease. An emerging approach is to detect developing preclinical disease before it becomes clinically apparent allowing interventions to be started earlier. This is an approach that has worked effectively in the area of cancer for a number of years and allows early treatment of detected disease. A variety of methods of detecting preclinical disease have been suggested and researched to differing degrees. There is evidence that natriuretic peptides are able to identify those with a variety of cardiovascular abnormalities including subclinical or silent cardiovascular disease and that increased levels are associated with cardiovascular mortality. However BNP is a very non-specific marker of cardiovascular abnormality so is not sufficient on its own to identify those at increased risk of cardiovascular disease. Cardiac and whole body magnetic resonance imaging is able to detect subclinical disease however imaging everybody for screening would be expensive and poor use of resources. Therefore “pre-screening” using a relatively low cost and widely available blood marker (BNP) could exclude those truly at low risk with a normal cardiovascular system and facilitate targeted more detailed phenotyping using more expensive and invasive whole-body contrast enhanced magnetic resonance imaging to detect a range of cardiovascular abnormalities (arterial disease, left ventricular hypertrophy, silent infarcts) that are associated with future clinical disease. This could potentially prevent future disease by facilitating targeted and individualised advice and treatment. The ability of a combination of these techniques to predict future clinical CVD in a large population of individuals at low or intermediate risk of CVD has not so far been assessed.

The Tayside Screening for Cardiac Events (TASCFORCE) study is investigating the ability of a screening programme using BNP and whole body contrast enhanced

magnetic resonance imaging comprising cardiac imaging and whole body angiography to detect subclinical cardiovascular disease and predict future clinical cardiovascular disease in a population at low or intermediate (<20% in 10 year) predicted risk of CVD.

2. Methods: The TASCFORCE study-screening for asymptomatic cardiovascular disease

2.1. Study design

The **TA**yside **SC**reening **FOR C**ardiac **E**vents (TASCFORCE) study is a prospective normal volunteer cardiovascular risk screening study (ISRCTN number: ISRCTN38976321). The protocol was approved by the Tayside Committee of Medical Research Ethics and can be accessed at http://www.controlled-trials.com/ISRCTN38976321/TASCFORCE. All study procedures were performed in accordance with Good Clinical Practice. Written informed consent for the study was obtained from each participant prior to enrollment in the study (appendix 3).

Men and women aged 40 years or older living in Tayside or Fife, Scotland, were eligible for participation.

Exclusion criteria were:

- known atherosclerotic disease,
- predicted increased risk of CVD requiring statin treatment, according to the Scottish Intercollegiate Guideline Network (SIGN) 97 Guideline[5] (≥20% in 10 years)
- BP greater than 145/90mmHg
- other accepted indication for statin therapy according to the investigators' current clinical practice (including familial hyperlipidaemia requiring drug therapy and known diabetes), any illness which in the doctor's opinion meant that the subject was unable to give informed consent.

Additionally a number of additional exclusion criteria were included to produce a population that could participate in a potential future statin intervention trial. These were:

- known primary muscle disease,
- significant biochemical abnormalities (such as acute liver disease or hepatic dysfunction with aspartate transaminase (AST) or alanine transaminase (ALT) greater than two times the upper limit of normal,
- other serious illness or significant abnormalities that may compromise the participant's safety or successful participation in the study,
- known alcohol abuse,
- participation in a clinical trial other than observational trials or registries concurrently or within 30 days prior to screening for entry to the study,
- pregnancy,
- breast-feeding,
- women of child-bearing potential not using adequate contraception.

Patients were also excluded if they were taking any of the following medications:

- over the counter statins,
- drugs known to be associated with rhabdomyolysis in combination with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors,
- drugs known to affect lipid levels,
- lipid-regulating drugs (probucol, fibrates and derivatives, bile acid sequestering resins).

2.2. Recruitment

Potential participants were recruited from a variety of sources. Ethically approved TASCFORCE leaflets (appendix 1) were handed out by research staff at appropriate public gatherings and events and were provided for members of the public to pick up at a range of sites throughout the region. Publicity campaigns, via press and radio coverage, and letters to subjects who had already agreed (and given written consent) to be contacted for such trials further raised awareness of the study. Participants were

also recruited from General Practice (GP) surgeries and large local employers. Potential participants were asked to use the contact details provided on the leaflets or letters to register their interest with the study team. Interested subjects were then contacted by study staff by telephone to answer questions about demographic details and the presence of any exclusion criteria. This allowed selection to be made of potentially eligible subjects who were sent an information sheet (see appendix) about the study and invited for screening visit 1.

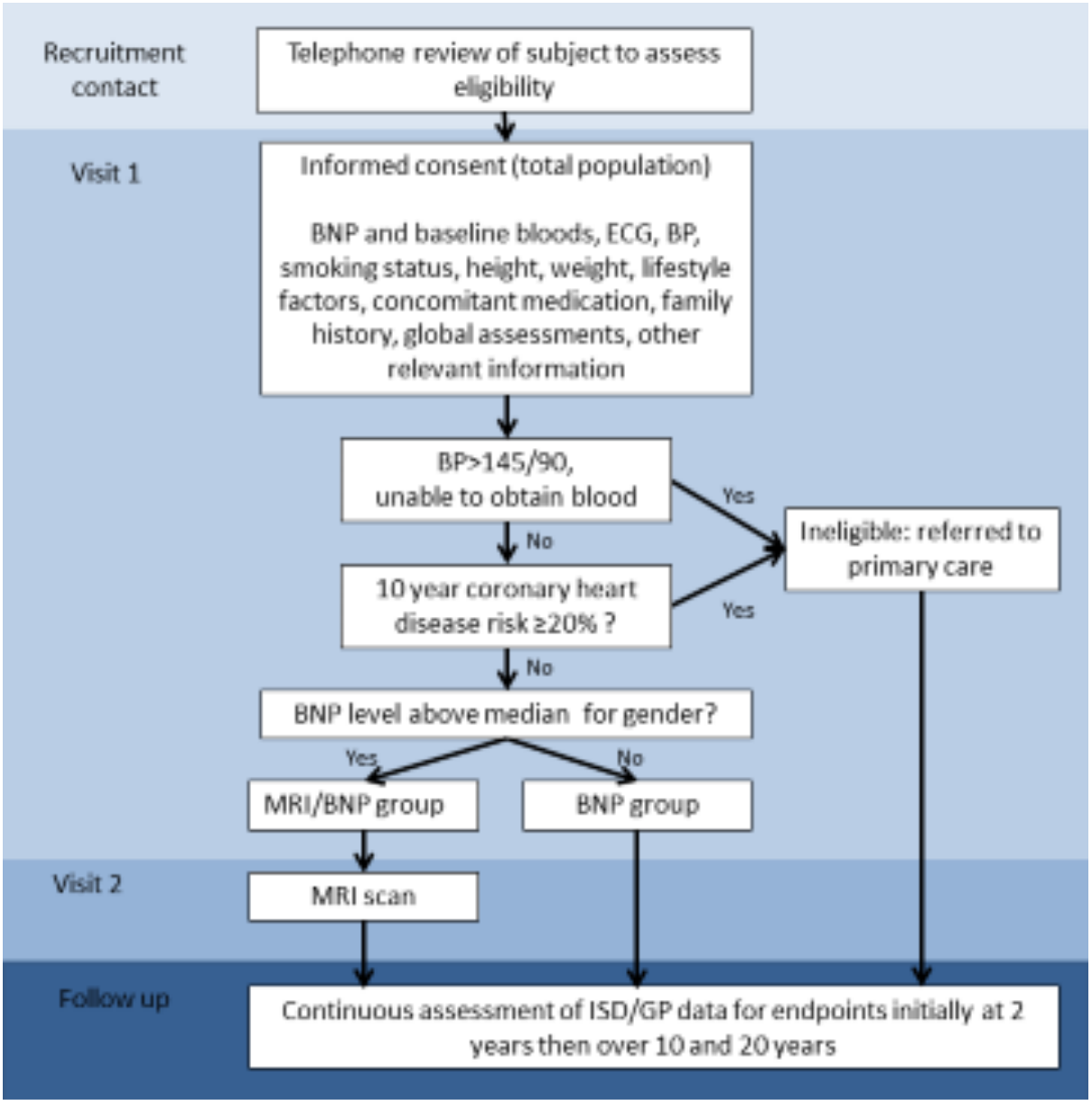
During the recruitment process pre-agreed 6-monthly checks were made of Scottish Index of Multiple Deprivation (SIMD), gender and age profile of the recruits so that future recruitment could be targeted to reflect the population from where they were drawn, i.e. Tayside. It is recognised that such screening trials may over recruit in the higher SIMD groups; by recruiting from GP surgeries within lower SIMD codes and from certain employers recruitment could be targeted to ensure under-represented groups were recruited pro-rata for the Tayside population. This aimed to produce a study population that represented the local regional population as a whole as closely as possible and included individuals from lower socio-economic status who are both frequently under-represented in clinical trials and often have poor engagement with health screening programmes.

2.3. Assessments

2.3.1. The Assessment for Eligibility

An overview of the flow of participants and activity at each stage is summarised in figure 2.1.

Figure 2.1: Flowchart giving overview of study design.



BNP=B-type natriuretic peptide, MRI=magnetic resonance imaging, ISD=Information and Statistics Division, Scotland, GP=General practice, ECG=electrocardiogram, BP=blood pressure.

2.3.2. Screening visit

Potentially eligible participants were assessed at visit 1. This visit was either at the Clinical Research Centre at Ninewells Hospital and Medical School, Dundee or for those who worked at one of the large local employers at their workplace. A formal assessment of inclusion and exclusion criteria was made (except for cardiovascular risk, BP and lipid profile which were checked after consent was given during the initial assessment – see below). If the subject was potentially suitable for inclusion explanations of the procedures were given along with the participant information sheet (appendix 2) and written informed consent (appendix 3) was obtained at this point.

The following information was obtained and documented on a case report form (CRF – see appendix 4): medical history, lifestyle risk factors (diet/exercise), risk perception question, family history of cardiovascular disease, smoking status, and concomitant medication. Exercise was classified as either none, 1-2 times per week, moderate 3-4 times per week or strenuous 5-7 times per week along with a qualitative description of the type of exercise. Diet was qualitatively described. The risk perception question was "compared with a person of your own age and sex, how would you rate your risk of having a heart attack or stroke in the next 10 years?" Participants were asked to answer either "much lower than average", "lower than average", "average", "higher than average" or "much higher than average". A family history of cardiovascular disease was defined as disease in a female first degree relative aged less than 65 years or male first degree aged less than 55 years. Smoking status was classified as either "never smoked", "ex-smoker" or "current smoker". If participants were ex-smokers or current smokers their average number of cigarettes, cigars or pipes smoked per day along with the number of years smoked was recorded. To convert other tobacco types to equivalent smoking of cigarettes 1 pipe was counted as 2.5 cigarettes, 1 Hamlet (or equivalent size) as 2.5 cigarettes, 1 Havana (or equivalent size) as 4 cigarettes and 1 café crème cigar (or equivalent size) as 1.5 cigarettes. Using participants' postcodes their decile of Scottish Index of Multiple Deprivation

(SIMD) was determined. SIMD is a tool used by the Scottish government to identify areas where individuals may experience multiple deprivation (not for identifying individuals who are deprived). Postcodes can be used to determine if someone lives in an area of increased risk of deprivation which has been shown to be associated with cardiovascular risk.[228]

Participants were examined to obtain their height, weight, waist circumference and blood pressure. Height and weight were measured using a vertical measuring stick and calibrated scales respectively. These measurements were used to calculate body mass index (BMI) by dividing weight in kilograms by height in metres squared. Waist circumference was measured using a flexible plastic measuring tape which were replaced at regular intervals to avoid stretching of the plastic. Participants were asked to lift their clothing to expose the abdominal area while standing. The narrowest waist level, or if this was not apparent, at the midpoint between the lowest rib and top of the iliac crest, was measured with the tape measure lying flat on the skin. This measurement was taken once for each participant. A 12 lead electrocardiogram (ECG) was recorded for each subject using ECG machines that were calibrated annually. Blood pressure was measured using a manual sphygmomanometer and stethoscope after the participant had been at rest for at least 15 minutes. It was measured in the left arm with the arm rested on a table at heart level. If the initial reading was greater than 145mmHg (systolic) or 90mmHg (diastolic) a second reading was taken. If this remained elevated a third reading was taken. If this was still elevated the participant was excluded from the study and referred to their GP for follow up an appropriate clinical management. If more than one reading was taken the lowest reading was used for calculations and data analysis. Those excluded due to hypertension did not have their full cardiovascular risk assessed.

Blood was obtained by venepuncture for analysis of lipid profile, glucose and B-type natriuretic peptide (BNP). Blood was collected in BD vacutainer tubes (Becton,

Dickinson and Company, Franklin Lakes, New Jersey, USA). Samples for the lipid and glucose assay were collected in a serum SST tube (silicone coated interior with clot activator and gel for serum separation) and for BNP in ethylenediaminetetraacetic acid (EDTA) tube. Glucose measurement was only started halfway through recruitment so blood glucose results are not available for all participants.

The lipid profile (random total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides – mmol/L) and glucose (mmol/L) were measured using the Alere Cholestech LDX analyser (Alere, Waltham, Massachusetts, USA). This machine also calculated the estimated 10 year coronary heart disease (CHD) risk using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines.[229] The method of lipid and glucose determination is explained in detail in product literature.[230] The inter-assay bias limits from the product literature were -1%, -2%, 0% and 0% for total cholesterol, HDL cholesterol, triglycerides and glucose respectively. The intra-assay coefficients of variation were 2.5%, 3.4%, 1.6% and 6.2% for total cholesterol, HDL cholesterol, triglycerides and glucose respectively.[230] The cassette separates the plasma from blood cells. A portion of the plasma then flowed to one side of the cassette where low and very low density lipoproteins were precipitated with dextran sulphate and magnesium acetate. The filtrate from that process were then passed to the glucose and HDL cholesterol reaction pads. Another portion of the plasma flowed to the total cholesterol and triglyceride reaction pads. Cholesterol esterase hydrolysed the cholesterol esters to free cholesterol and the corresponding fatty acid. Cholesterol oxidase, in the presence of oxygen, oxidized free cholesterol to cholest-4-ene-3-one and hydrogen peroxide. In a reaction catalyzed by horseradish peroxidase, the peroxide reacted with 4-aminoantipyrine and N-ethyl-N-sulfohydroxypropyl-m-toluidine, sodium salt (TOOS) to form a purple-coloured quinoneimine dye proportional to the total cholesterol and HDL cholesterol concentrations of the sample. Triglycerides were measured by an enzymatic method based on the hydrolysis of triglycerides by lipase to

glycerol and free fatty acids. Glycerol, in a reaction catalyzed by glycerol kinase, was converted to glycerol-3-phosphate. In a third reaction, glycerol-3-phosphate was oxidized by glycerol phosphate oxidase to dihydroxyacetone phosphate and hydrogen peroxide. The colour reaction utilizing horseradish peroxidase was the same as for the total cholesterol and HDL cholesterol. LDL cholesterol level is calculated using the Friedewald calculation (LDL= Total cholesterol – HDL – triglycerides/2.17).[231] Levels of triglycerides lower than 0.51mmol/l could not be determined by the assay and levels above 4.51mmol/l can result in inaccurate estimation of LDL levels. Therefore if the triglycerides fell outside this range the machine was unable to calculate the LDL level. Glucose was measured by an enzymatic method that used glucose oxidase to catalyse the oxidation of glucose to gluconolactone and hydrogen peroxide. The colour reaction utilizing horseradish peroxidase was again the same as that for total cholesterol, HDL cholesterol and triglycerides. The resultant colour in all of the reactions was measured by reflectance photometry.

BNP levels (pg/ml) were measured using the Alere Triage BNP assay (Beckman Coulter, Inc, Brea, California, USA) with an Alere Triage MeterPro (Alere, Waltham, Massachusetts, USA). The BNP assay was a two-site immunoenzymatic assay using mouse monoclonal anti-human BNP antibody-alkaline phosphatase conjugate and paramagnetic particles coated with mouse omniclonal anti-human BNP antibody. Following incubation materials bound to the solid phase were held in a magnetic field and unbound materials were washed away. The machine then used a luminometer to measure light generated (directly proportional to the concentration of BNP) by a reaction from addition of a chemiluminescent substrate. The test used plasma using ethylenediaminetetraacetic acid (EDTA) as the anticoagulant. The machine was calibrated as advised by the product literature. The intra-assay coefficient of variation for low level BNP (as in the TASCFORCE study) from the product literature was 9.2%.[232]

Blood was also obtained for storage in the Tayside Tissue biobank for later analysis of endothelial and vascular markers. For those subjects who consented to participate in a genetic sub-study further blood was obtained for DNA analysis in EDTA tubes. These samples were frozen for analysis at a later date.

2.3.3. Cardiovascular risk estimation

Subjects found to have a CHD risk of greater than or equal to 20% over 10 years as assessed by the near patient testing equipment using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines[229] and who were therefore potentially eligible for statin treatment under current guidelines, were ineligible to continue in the study. Subjects were also ineligible to proceed if they had a blood pressure greater than 145/90 mmHg (after at least three readings), if blood was impossible to obtain by venepuncture or if the bedside machine was unable to calculate their risk score (i.e. it was very high). These subjects were then asked for written informed consent to have their records electronically tagged to be followed up in the same way as participants in the main study (see below). Ineligible subjects were informed of their indication for risk factor management by the study nurse/doctor, given a copy of their results and asked to attend their General Practitioner for formal review. The GP was informed of any risk factor(s) using a standard letter e.g. all subjects found to be hypertensive (BP<145/90mmHg) or who had a predicted coronary heart disease risk of ≥20% over 10 years. Those with estimated risk levels below that recommended for treatment and with a BP<145/90mmHg were enrolled to the study. In line with local clinical guidelines those with a random blood glucose level >7mmol/l (including those with a level .11mmol/l) were advised of the need to have this followed up with a repeat fasting sample at their GP surgery to determine if they had diabetes. Such participants' GPs were also informed of their random blood glucose result. Because glucose testing was not offered to about half the participants (it was introduced partway through recruitment) an increased level was not used to exclude people from the study.

All participants (both those who were eligible and those not eligible due to increased CHD risk or hypertension) received counselling on modifiable risk factors. This took the form of general information about blood pressure and cholesterol supplemented by individualised information based on smoking history and cholesterol results. Verbal information was supplemented by written material about smoking, healthy diet and blood pressure prepared by the British Heart Foundation. All participants' GPs were informed about their blood results, blood pressure and BMI results and whether repeat samples and/or clinical review by the GP was advised.

ASSIGN scores[41] were calculated for all eligible participants by using the demographic and cardiovascular risk variables collected and inputting them in the ASSIGN score algorithm. This was performed retrospectively after all participants had been recruited and not at the time of recruitment.

2.3.4. BNP measurement and allocation to MRI group

Once 200 subjects had been recruited the median BNP result (16.5pg/ml) was calculated for these 200 subjects. Those with a BNP greater than this median were allocated to the MRI/BNP group and invited to attend for an MRI scan at visit 2 (see below). The subjects not in the MRI/BNP group were called the BNP population. A further planned assessment was performed after 1000 participants had been recruited and on this occasion it was observed that the median BNP was higher for women than men (16.4pg/ml v 8.2pg/ml) resulting in very few men being allocated to the MRI/BNP group. The trial steering committee therefore decided to allocate subjects based on their gender specific median BNP value and the protocol was amended accordingly. Those subjects recruited early who were allocated to the BNP group but would be eligible for an MRI based on their gender specific median were recalled and asked to undergo MRI scanning. If the delay to this was greater than three months they had their BP, BNP, lipid profile and glucose rechecked to ensure continued eligibility and also had their height and weight remeasured. Hypertension is more prevalent with

increasing age and lipid profiles and BMI can change over time due to changes in dietary intake and exercise profile. Natriuretic peptide levels increase with age[141] and have also been shown to change over time and can reflect dynamic changes in cardiovascular risk.[169]

A number of participants were also initially excluded from having an MRI scan on the basis of a metal in situ e.g. previous penetrative eye injury or exposure to metal fragments but would otherwise have been deemed eligible as per their BNP level. After consideration by the trial steering committee it was decided that such subjects should be recalled, as their risk during MRI was low. If interested in proceeding with an MRI scan research staff re-established their eligibility and MRI safety status if necessary by having an orbital x-ray. As with the recalled patients above, where the duration between Visit 1 and the proposed Visit 2 was greater than 3 months, subjects had their cholesterol, glucose and BNP levels and BP reassessed to ensure continued eligibility. Height and weight was re-measured.

Also recruited was a substudy of participants of South Asian ethnicity which was incorporated in the protocol to examine potential differences in risk and subclinical disease in this ethnic group compared to a Caucasian population. This also ensured representation of this group within the whole study population. South Asians enrolled in this substudy were invited for an MRI scan regardless of their BNP result.

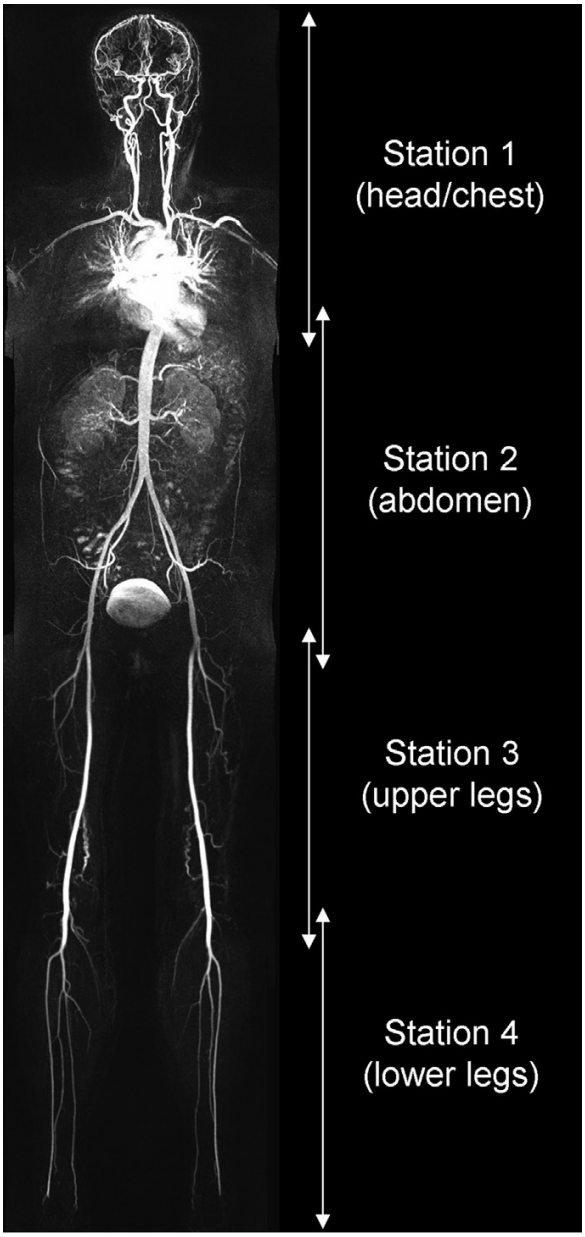
2.3.5. MRI acquisition technique

Subjects allocated to the MRI/BNP group had a whole body contrast enhanced MRI scan (WB CE-MRI) comprising cardiac (CMR) and whole body MRI angiogram (MRA) performed at visit 2 at the clinical research centre at Ninewells Hospital and Medical School, Dundee. The validation of the technique has been described in detail in an earlier paper.[233] The scans were performed in an integrated examination on a 32-channel 3.0 Tesla Magnetom Trio scanner (Siemens, Erlangen, Germany). Patients were positioned head first in a supine position. Six sets of surface coils were used to

cover the body: head matrix coil (12 elements), neck matrix coil (4 elements), 2x body matrix coils (each with 6 elements), peripheral angiography coil (16 elements), and spine matrix coil (up to 24 elements depending on patient size) (see figure 2.7). Initial three-plane “localiser” scout images were acquired for the MRA using 500 mm field-of-view (FOV) gradient echo fast low-angle shot (FLASH) sequence in the coronal, sagittal, and transverse planes from head to foot. This provided 4 anatomical stations: head and chest, abdomen, upper legs and lower legs (figure 2.8). Localizer images were positioned with an “overlap” between each FOV of at least 75 mm but adjustable according to patient height. Localizer TurboFLASH images of the heart in the two-chamber, four-chamber and short axis (SA) orientations were also acquired. All 3D acquisitions were then planned using these scout images.

Figure 2.2: Participant undergoing whole body CE-MRI scan.

Figure 2.3: MRI stations/fields of view (FOV)



Station 1 and 4 images are acquired after the first injection of contrast agent. Station 2 and 3 images are acquired after the second injection of contrast agent. Overlap between stations was at least 75mm but varied with participant height.

Protocol section 1-cine imaging and cardiac MRI and LV function

ECG-gated segmented breath-hold cine true fast imaging with steady state precision (TrueFISP) images were acquired in the LV 4 chamber and 2 chamber orientations. A stack of short axis images from the atrioventricular ring to the left ventricular apex were then acquired using 2D ECG-gated breath-hold segmented CINE TrueFISP sequence with retrospective gating. The imaging parameters included repetition time

3.4milliseconds, echo time of 1.5milliseconds and flip angle 50°. Each slice was 6mm thick with a 4mm gap. Two slices were taken per breath hold of less than 15 seconds and scan time was minimized using parallel imaging generalised autocalibrating partially parallel acquisition (GRAPPA) factor of two. Imaging parameters for all the scan protocol stages are summarised in table 2.1.

Table 2.1: Imaging parameters for all sequences run within the combined CMR and MRA protocol.

Protocol Section	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**
Description	CINE	CINE	WB-MRA	WB-MRA	TI-Scout	PSIR	WB-MRA	WB-MRA
Location	Heart	Heart LV	Station 1	Station 4	Heart LV	Heart LV	Station 2	Station 3
Sequence	2D TFi	2D TFi	3D TFl	3D TFl	2D TFi	2D PSIR	3D TFl	3D TFl
Cardiac Phases	25	25	-	-	Variable	-	-	-
ECG Gating	Retro	Retro	-	-	Pro	Pro	-	-
Lines/segment	14	26	-	-	9	25	-	-
Orientation	4ch & 2ch	SA	Coronal	Coronal	SA	SA	Coronal	Coronal
TR/TE (ms)	3.37/1.48	3.37/1.48	2.68/1.00	2.61/0.96	3.11/1.99	5.21/1.99	2.60/0.96	3.47/1.21
FA (^{o})	>50	>50	19	22	35	20	16	37
FOV (mm)	>360	>360	360x500	360x500	>360	>360	344x500	344x500
Phase FOV (%)	84.4	84.4	71.9	68.8	81.3	75.0	68.8	71.9
Slice thickness (mm)	6	6	1.1	1	8	6	1.3	1.4
Number Slices	1	2	96	80	1	2	96	96
Resolution (pixels)	216x256	173x256	313x512	277x448	78x192	144x256	264x512	242x448
Voxel Size (mm)	Variable	Variable	1.1x1.0x1.1	1.2x1.1x1.0	Variable	Variable	1.3x1.0x1.3	1.5x1.1x1.4
i-PAT	x2	x2	x3	x3	-	x2	x3	x3
K-space	Linear	Linear	3D centric	3D centric	Centric	Linear	3D centric	3D centric
BW (Hz/pix)	930	930	700	700	965	287	700	740
Scan time (s)	<20	<20	18	14	<20	<20	14	16

LV = left ventricle, TFi = TrueFISP, TFl = TurboFLASH, PSIR = phase sensitive inversion recovery, Retro = Retrospective, Pro = Prospective, 4ch = Four Chamber, 2ch = Two Chamber, SA = Short Axis, TR = Repetition Time, TE = Echo Time, FA = Flip Angle, FOV = Field of View, i-PAT = integrated Parallel Acquisition Technique, BW = Bandwidth.

Protocol section 2-WB-MRA stations 1 and 4

The technique for whole body contrast enhanced magnetic resonance angiography (WB CE-MRA) has been optimised and validated by the TASCFORCE research group and is described in detail in an earlier publication.[203] Unenhanced CE-MRA “mask” data were acquired for each station using a 3D TurboFLASH sequence, and the scanner table was preset to move at a rate of 50 cm/s. 10 ml of 0.05 mmol/ml gadoteric acid (Dotarem, Guerbet, France) followed by 20 ml saline flush was delivered at the left or right antecubital fossa using a Spectris Solaris power injector (MedRad, Pittsburgh, PA, USA) at a rate of 1.5 ml/s. While standard contrast doses were used as part of the protocol, average patient weights in each group were used to calculate a contrast agent dose per weight for each group. Timing was controlled by a coronal 2D Care Bolus acquisition (MR fluoroscopy), and the contrast-enhanced acquisition for station 1 commenced when contrast agent arrival was noted at the top of the aortic arch. Post-contrast data for station 4 were acquired immediately after completion of station 1, and these were acquired three times consecutively to account for variable arterial transit times to the distal leg vessels.

Protocol section 3-cardiac MRI of myocardial viability with phase-sensitive inversion recovery (PSIR)

An ECG-gated segmented breath-hold 2D inversion-recovery prepared CINE TrueFISP “TI-Scout” sequence was implemented (in a central short-axis position) 8-10 min after initial contrast medium injection in order to identify the null point inversion time for the myocardium. Subsequently, at a mean of 11 min post-contrast medium administration (range 9-16 minutes) a short-axis stack of ECG-gated segmented 2D PSIR images were acquired in order to highlight any late gadolinium enhancement (LGE) within the myocardium. The mean inversion time used was 376ms (range 300-450 ms).

Protocol section 4-WB-MRA stations 2 and 3

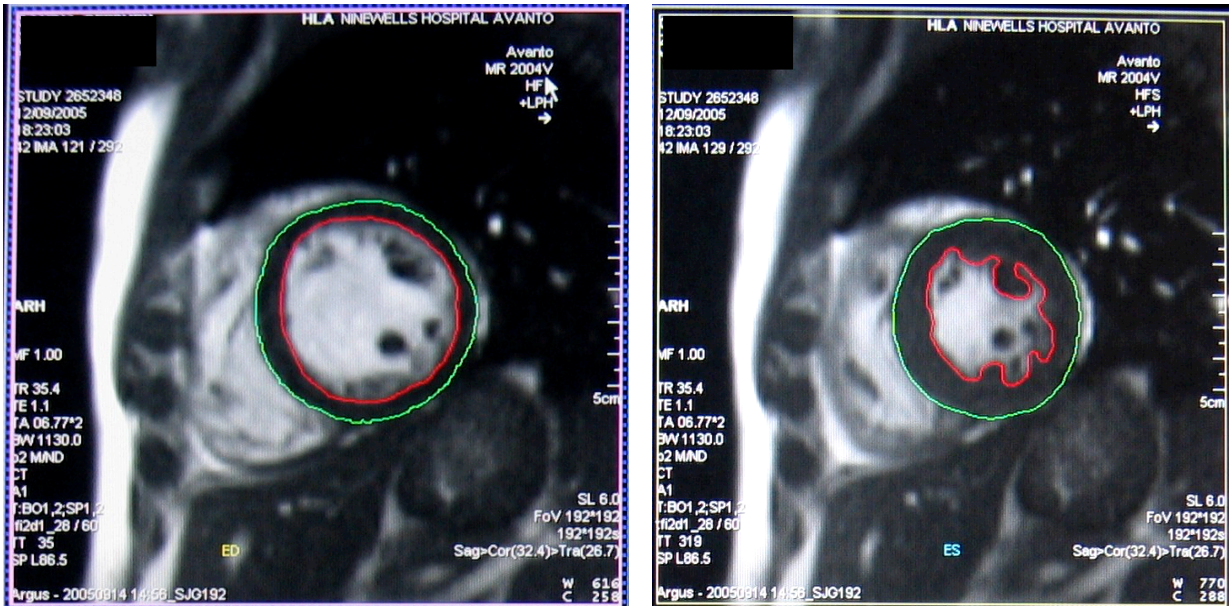
Unenhanced 3D Turbo-FLASH “mask” data were acquired for each station. The second contrast agent dose of 15ml was infused at 1.5 ml/s followed by a 20 ml saline flush using the same equipment as in protocol section 1. Timing was again controlled by 2D Care Bolus (coronal plane abdominal aorta), and post-contrast scans for station 2 were triggered when the bolus could be seen arriving in the abdominal aorta. Due to the presence of contrast from the first injection, the arrival of the contrast bolus in the abdominal aorta was not always obvious at the second injection. Therefore, the timing information from the first injection was used in conjunction with MR fluoroscopy to start the post-contrast acquisitions of stations 2 and 3, after the mask images had been acquired. The timing was used to identify when contrast was expected in the abdominal aorta and the scan was started as a brighter ‘‘blush’’ was seen on the fluoroscopic acquisition. Post-contrast data for station 3 were acquired immediately after completion of the station 2 sequence. The average time between first and second contrast agent injections was 19 min (range 15-34 min). Finally, the pre- and post-contrast WB-MRA data were subtracted and the resulting images were stitched using a multi-modality work platform (MMWP; Composing, Siemens, Erlangen, Germany). Multiplanar reconstructions (MPR) and maximum intensity projections (MIP) were also generated for further radiological interpretation.

2.3.6. MRI left ventricular quantification

CMR images were analysed offline by one of six blinded observers using commercial software (‘Argus’, Siemens Multi-modality Work Platform, version VB 15 and VB 17). Electronic region of interest (ROI) contours were placed manually around endocardial and epicardial left ventricular borders on all CMR image slices at end-diastole and end-systole that were identified to contain 50% or more full-thickness myocardium (see figure 2.9). Papillary muscles were included in the LV mass if the muscle structure was indistinguishable from the myocardial wall, but otherwise assigned to the left ventricular blood pool. All myocardium (whether normal or displaying delayed gadolinium

enhancement) was included. The process of contour placement was repeated such that every patient dataset at both time-points was analysed twice in order to optimize the measurement precision (no participants were imaged more than once to check reproducibility of image acquisition). From these contours, quantitative measurement of the areas of the left ventricular muscle and left ventricular blood pool were calculated. These areas were then multiplied by the slice thickness and the slices summed to derive the left ventricular muscle and left ventricular blood pool volumes. These were then used to calculate end-diastolic volume, end-systolic volume, stroke volume and ejection fraction. Cardiac output was calculated by multiplying stroke volume by heart rate and LVM was calculated by multiplying the left ventricular muscle volume at end diastole by the specific gravity of myocardium (1.05g/ml).

Figure 2.4: Defining endocardial border (red) and epicardial border (green) at end of diastole (left) and end of systole (right)



The LVM was indexed (LVMI) to account for body size using a selection of techniques reported in the literature. This was performed by dividing LVM by the index value. The index values used were body surface area (BSA) calculated using the Dubois formula, BSA calculated using the Mosteller formula, height, height$^{1.7}$ and height$^{2.7}$.

The detection of gadolinium enhanced infarcts was performed manually on standard image analysis workstations (using Carestream PACS v10.1 on Barco 3MP monitors) based on an established myocardial segmentation and nomenclature using a 17 segment model.[234]

2.3.7. MRI angiogram scoring technique

WB CE-MRA images were analysed by one of four blinded observers on standard image analysis workstations (using Carestream PACS v10.1 on Barco 3MP monitors) using the original source (3D FLASH post-contrast) images, along with subtracted MPRs and MIPs. The MRI whole-body arterial tree for every patient was divided anatomically into 31 segments: right and left internal carotid arteries, right and left vertebral arteries, right and left common carotid arteries, innominate artery, right and left subclavian arteries, aortic arch, thoracic aorta, abdominal aorta, coeliac artery, superior mesenteric artery, inferior mesenteric artery, right and left renal arteries, right and left iliac arteries, right and left femoral arteries, right & left profunda femoris arteries, right and left popliteal arteries, right and left anterior tibial arteries, right and left common peroneal arteries, and right and left posterior tibial arteries. Each arterial segment was assessed for the presence of luminal stenosis and/or aneurysm and allocated a code in a spreadsheet (table 2.2). If any arterial segment contained more than one luminal abnormality then the more severe abnormality was scored. Aneurysms were counted if they were greater than 50% wider than the proximal normal artery. A score was then allocated for each arterial segment (see table 2.2) based on the severity of any stenosis and/or aneurysm. This score reflected the degree of stenosis with an extra point being given for the presence of aneurysm. If a segment was uninterpretable because of poor image quality or if it was not included in the scan because of stopping of the scan before completion (e.g. due to claustrophobia) it was not allocated a numeric score. The scores for each arterial segment were then added together to give a total whole body atheroma score (WBAS). To account for uninterpretable segments the total score was divided by the number of interpretable

segments to produce a normalised whole body atheroma score. A standardised atheroma score (SAS) was calculated using the following equation where n is the number of interpretable segments:

$$SAS = \left[\left(\frac{\sum score}{n} \right) \times \frac{1}{4} \right] \times 100$$

Regional standardised atheroma scores were also calculated to reflect possible different disease distributions. The regions were: head and neck (internal carotid, vertebral, innominate, common carotid, and subclavian arteries), aorta (aortic arch, thoracic aorta, abdominal aorta), abdominal (coeliac trunk, superior and inferior mesenteric and renal arteries), ileofemoral (common, external and internal iliac arteries, common and superficial femoral arteries and profunda femoris arteries) and run off arteries (popliteal, anterior tibial, posterior tibial and peroneal arteries).

Table 2.2: Coding and scoring for WB CE-MRA arterial segments.

Abnormality	Code	Score ascribed to contribute to whole body atheroma score
Normal	0	0
<50% stenosis	1	1
51-70% stenosis	2	2
71-99% stenosis	3	3
Occluded segment	4	4
Aneurysm but no stenosis	5	1
Aneurysm and <50% stenosis	6	2
Aneurysm and 51-70% stenosis	7	3
Aneurysm and 71-99% stenosis	8	4
Aneurysm and occlusion	9	5

2.3.8. MRI angiogram interpretation validation

The angiograms were assessed by one of four observers so it was important that inter-observer reproducibility was assessed to ensure that scoring was not dependent on individual observers. Intra-observer reproducibility was also assessed to further validate the technique. To achieve this 48 scans were randomly selected by a trial statistician. These 48 scans were all assessed by all four WB CE-MRA observers to allow assessment of inter-observer reproducibility. A consensus score was determined for each segment based on the most common score if there was disagreement between observers. If there was no clear consensus from the initial assessments a further review by at least 2 of the observers produced a “consensus score” for that segment.

Each observer also assessed a subset of 12 scans twice to assess intra-observer reproducibility. The second assessment was performed at least 1 month after the first assessment to reduce the impact of learning.

2.3.9. MRI incidental findings

As would be expected when scanning a large number of individuals some MRI scans revealed incidental findings ranging from congenital anatomical abnormalities to previously undiagnosed pathology such as potential tumours. All scans were reported by a trained radiologist shortly after being acquired. When an abnormality was found, which in the opinion of the radiologist merited further clinical assessment or investigation, the incidental finding was reviewed by one of the study doctors. Depending on the nature of the finding the participant was either invited to have a further clinical assessment by one of the study doctors or referred to their GP for further review. The participant was informed of this by a telephone call. Further investigation and management was then arranged as appropriate. Summaries of the radiological incidental findings found are summarised along with the further clinical

activity (clinical reviews, medication commencement, further imaging) required as a result of the findings.

2.4. Follow up

2.4.1. Health Informatics Centre data linkage

Participants' health records (both those who failed screening and those who were eligible for the study) have been electronically tagged with the Scottish Office's Information Services Division (ISD) via the Health Informatics Centre (HIC) at the University of Dundee as well as at their local hospital Trusts' Medical Information departments. Using anonymised data linkage by HIC follow up data on a variety of clinical outcomes was planned to be obtained 2 years after recruitment initially then at regular intervals for up to 20 years. Ethical approval for this was obtained and this was explicit in the participant information sheet. Data obtained comprised:

- all details of hospital admissions including the diagnoses made and procedures performed during the admissions,
- all details of prescriptions issued by the participants general practitioners,
- all details of deaths registered with the general registrar office (GRO) including details of cause of death.

2.4.2. Outcome measures

The primary predefined aim of the study was the ability of increased left ventricular mass, as assessed by contrast enhanced MRI, to predict future CV events. It is recognised that less than half of the total study population were imaged as their selection was based on BNP level however the trial steering committee felt that this measure had the best existing evidence base and was most likely to be predictive of future events.

Secondary aims of the study were:

1. the ability to predict future CV events and disease using whole body contrast enhanced magnetic resonance angiography (WB CE-MRA) in the MRI/BNP group;
2. the ability to predict future CV events and disease using a combination of BNP levels and WB CE-MRA;
3. the ability to predict future CV events and disease using BNP and other biomarkers in both the MRI/BNP and BNP groups.

Using record linkage as described above the incidence of a number of endpoints were determined for both the study population and those who failed screening initially at 2 years from end of study recruitment and regularly thereafter. The time since recruitment that these events occur was determined. The endpoints were determined using (international classification of disease version 10 (ICD-10) codes and procedures using Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision) (OPCS-4) codes. These are codes used by hospitals to record all diagnoses (ICD) and procedures or operations (OPCS) that are relevant to an individual during a hospital visit. Endpoints of interest were myocardial infarction (fatal and non-fatal), hospitalisation for angina, requirement for any endovascular procedure (e.g. angioplasty, stent, by-pass grafting), stroke, sudden death and all-cause mortality. The ICD-10 codes of interest are summarised in table 2.3 and the OPCS-4 codes in table 2.4. Analyses were performed separately including and excluding peripheral arterial disease (PAD) diagnoses and procedures. Those codes for PAD are highlighted in grey.

Table 2.3: ICD-10 end point codes

Code	**Diagnosis**
I20.0	Unstable angina
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I21 (including all subdivisions)	Acute myocardial infarction
I24.0	Coronary artery thrombosis not resulting in myocardial infarction
I24.8	Other forms of acute ischaemic heart disease
I24.9	Acute ischaemic heart disease, unspecified
I25.0	Atherosclerotic cardiovascular disease, so described
I25.1	Atherosclerotic heart disease
I25.6	Silent myocardial ischaemia
I46.1	Sudden cardiac death, so described
I61 (including all subdivisions)	Intracerebral haemorrhage
I63.0	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	Cerebral infarction due to embolism of precerebral arteries
I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I64	Stroke, not specified as haemorrhage or infarction
I70 (including all subdivisions)	Atherosclerosis

Table 2.4: OPCS-4 codes

Code	Procedure
K23.4	Revascularisation of wall of heart
K40 (all subdivisions)	Saphenous vein graft replacement of coronary artery
K41 (all subdivisions)	Other autograft replacement of coronary artery
K42 (all subdivisions)	Allograft replacement of coronary artery
K43 (all subdivisions)	Prosthetic replacement of coronary artery
K44 (all subdivisions)	Other replacement of coronary artery
K45 (all subdivisions)	Connection of thoracic artery to coronary artery
K46.1	Double implantation of mammary arteries into heart
K46.2	Double implantation of thoracic arteries into heart NEC
K46.3	Implantation of mammary artery into heart NEC
K46.4	Implantation of thoracic artery into heart NEC
K46.5	Revision of implantation of thoracic artery into heart
K46.8	Other specified other bypass of coronary artery
K46.9	Unspecified other bypass of coronary artery
K47.1	Endarterectomy of coronary artery
K48.3	Open angioplasty of coronary artery
K48.4	Exploration of coronary artery
K48.8	Other specified other open operations on coronary artery
K48.9	Unspecified other open operations on coronary artery
K49 (all subdivisions)	Transluminal balloon angioplasty of coronary artery
K50.1	Percutaneous transluminal laser coronary angioplasty
K50.2	Percutaneous transluminal coronary thrombolysis using streptokinase
K50.4	Percutaneous transluminal atherectomy of coronary artery
K50.8	Other specified other therapeutic transluminal operations on coronary artery
K50.9	Unspecified other therapeutic transluminal operations on coronary artery
K75 (all subdivisions)	Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
L26.1	Percutaneous transluminal balloon angioplasty of aorta
L26.2	Percutaneous transluminal angioplasty of aorta NEC

Continued on next page

Table 2.4 continued

L26.5	Percutaneous transluminal insertion of stent into aorta
L26.6	Transluminal aortic stent graft with fenestration NEC
L26.7	Transluminal aortic branched stent graft NEC
L29	Reconstruction of carotid artery
L29.1	Replacement of carotid artery using graft
L29.2	Intracranial bypass to carotid artery NEC
L29.3	Bypass to carotid artery NEC
L29.4	Endarterectomy of carotid artery and patch repair of carotid artery
L29.5	Endarterectomy of carotid artery NEC
L29.6	High-flow interposition extracranial to intracranial bypass from external carotid artery to middle cerebral artery
L29.7	Bypass of carotid artery by anastomosis of superficial temporal artery to middle cerebral artery
L29.8	Other specified reconstruction of carotid artery
L29.9	Unspecified reconstruction of carotid artery
L30.1	Repair of carotid artery NEC
L30.3	Open embolectomy of carotid artery
L30.8	Other specified other open operations on carotid artery
L30.9	Unspecified other open operations on carotid artery
L31.1	Percutaneous transluminal angioplasty of carotid artery
L31.3	Endovascular repair of carotid artery
L31.4	Percutaneous transluminal insertion of stent into carotid artery
L31.8	Other specified transluminal operations on carotid artery
L31.9	Unspecified transluminal operations on carotid artery
L34.3	Open embolectomy of cerebral artery
L35.3	Percutaneous transluminal insertion of stent into cerebral artery
L35.8	Other specified transluminal operations on cerebral artery
L35.9	Unspecified transluminal operations on cerebral artery
L37	Reconstruction of subclavian artery
L37.1	Bypass of subclavian artery NEC
L37.2	Endarterectomy of vertebral artery
L37.3	Endarterectomy of subclavian artery and patch repair of subclavian artery
L37.4	Endarterectomy of subclavian artery NEC
L37.8	Other specified reconstruction of subclavian artery
L37.9	Unspecified reconstruction of subclavian artery
L38.3	Open embolectomy of subclavian artery

Continued on next page

Table 2.4 continued

L39.1	Percutaneous transluminal angioplasty of subclavian artery
L39.2	Percutaneous transluminal embolectomy of subclavian artery
L39.5	Percutaneous transluminal insertion of stent into subclavian artery
L39.8	Other specified transluminal operations on subclavian artery
L39.9	Unspecified transluminal operations on subclavian artery
L41.2	Bypass of renal artery
L41.3	Replantation of renal artery
L41.4	Endarterectomy of renal artery
L41.5	Translocation of branch of renal artery
L41.6	Patch angioplasty of renal artery
L41.8	Other specified reconstruction of renal artery
L41.9	Unspecified reconstruction of renal artery
L42.1	Open embolectomy of renal artery
L43.1	Percutaneous transluminal angioplasty of renal artery
L43.2	Percutaneous transluminal embolectomy of renal artery
L43.5	Percutaneous transluminal insertion of stent into renal artery
L43.8	Other specified transluminal operations on renal artery
L43.9	Unspecified transluminal operations on renal artery
L45 (all subdivisions)	Reconstruction of other visceral branch of abdominal aorta
L46.1	Open embolectomy of visceral branch of abdominal aorta NEC
L47.1	Percutaneous transluminal angioplasty of visceral branch of abdominal aorta NEC
L47.4	Percutaneous transluminal insertion of stent into visceral branch of abdominal aorta NEC
L47.8	Other specified transluminal operations on other visceral branch of abdominal aorta
L47.9	Unspecified transluminal operations on other visceral branch of abdominal aorta
L50 (all subdivisions)	Other emergency bypass of iliac artery
L51 (all subdivisions)	Other bypass of iliac artery
L52.1	Endarterectomy of iliac artery and patch repair of iliac artery
L52.2	Endarterectomy of iliac artery NEC
L53.2	Open embolectomy of iliac artery
L54.1	Percutaneous transluminal angioplasty of iliac artery
L54.2	Percutaneous transluminal embolectomy of iliac artery
L54.4	Percutaneous transluminal insertion of stent into iliac artery

Continued on next page

Table 2.4 continued

L54.8	Other specified transluminal operations on iliac artery
L54.9	Unspecified transluminal operations of iliac artery
L58 (all subdivisions)	Other emergency bypass of femoral artery
L59 (all subdivisions)	Other bypass of femoral artery
L60 (all subdivisions	Reconstruction of femoral artery
L62.2	Open embolectomy of femoral artery
L63.1	Percutaneous transluminal angioplasty of femoral artery
L63.2	Percutaneous transluminal embolectomy of femoral artery
L63.5	Percutaneous transluminal insertion of stent into femoral artery
L63.8	Other specified transluminal operations on femoral artery
L63.9	Unspecified transluminal operations on femoral artery
L66.1	Percutaneous transluminal arterial thrombolysis and reconstruction
L66.2	Percutaneous transluminal stent reconstruction of artery
L66.5	Percutaneous transluminal balloon angioplasty of artery
L66.7	Percutaneous transluminal placement of peripheral stent in artery
L66.8	Other specified other therapeutic transluminal operations on artery
L66.9	Unspecified other therapeutic transluminal operations on artery
L68.1	Endarterectomy and patch repair of artery NEC
L68.2	Endarterectomy NEC
L70.1	Open embolectomy of artery NEC
L71.1	Percutaneous transluminal angioplasty of artery
L71.2	Percutaneous transluminal embolectomy of artery
L71.5	Percutaneous transluminal dilation of artery
L71.6	Percutaneous transluminal thrombolysis of artery
L71.7	Percutaneous transluminal atherectomy
L71.8	Other specified therapeutic transluminal operations on other artery
L71.9	Unspecified therapeutic transluminal operations on other artery
L76 (all subdivisions)	Endovascular placement of stent
L89 (all subdivisions)	Other endovascular placement of stent

For those who died during follow up underlying cause of death, as recorded on death certificates, was provided by HIC/ISD supplemented by information from hospital records, including post-mortem examinations, if performed.

Data on prescribing was also obtained from GP records (via HIC) to determine if and when preventative cardiovascular medication was prescribed for both the eligible population and screen fail population. These were identified by British National Formulary (BNF) codes. The codes of interest are shown in table 2.5.

Table 2.5: Cardiovascular medication of interest at follow up

BNF code	**Drug**
2.1.1	Digoxin
2.2.1	Thiazides and related diuretics
2.2.2	Loop diuretics
2.2.3	Potassium sparing diuretics and aldosterone antagonists
2.2.4	Potassium sparing diuretics with other diuretics
2.2.8	Diuretics with potassium
2.4	Beta-adrenoceptor blocking drugs
2.5.2	Centrally acting antihypertensive drugs
2.5.4	Alpha-adrenoceptor blocking drugs
2.5.5 (including subgroups 2.5.5.1, 2.5.5.2, 2.5.5.3)	Drugs affecting the renin angiotensin system
2.6.1	Nitrates
2.6.2	Calcium-channel blockers
2.6.3	Other antianginal drugs
2.6.4	Peripheral vasodilators and related drugs
2.8.2	Oral anticoagulants
2.9	Antiplatelet drugs*
2.12	Lipid regulating drugs

BNF = British National Formulary. *Analysis was performed with and without aspirin as this is used for many non-cardiovascular indications.

2.5. Data entry and management

Data from the screening visit was entered on the CRF and transcribed to a password protected Access database (Microsoft Corporation, Redmond, USA). Data for the left ventricular assessments and WB CE-MRAs were entered on separate password-protected Excel spreadsheets (Microsoft Corporation, Redmond, USA) as the images were assessed. Once all image analysis had been completed demographic, risk factor and imaging data was merged in a single password protected Excel spreadsheet which was securely sent to the Health Informatics Centre (HIC) for follow up data linkage. HIC anonymised the data by ascribing a unique identifier (prochi) to each participant and rounding their date of birth to the nearest three months. The same prochi identifiers were used for the follow up data provided by HIC. This allowed linkage of the various pieces of data to allow statistical analysis to be performed. The anonymised data was placed in a secure server within HIC (Safehaven) where linkage and analyses were performed.

Before statistical analysis and data linkage was performed the data in the databases was cleansed to ensure it was accurate and as complete as possible. This was performed by ML and took a period of approximately 6 months although as analysis began further inaccuracies in the data were discovered requiring cross-checking and correction. Where inaccuracies, suspected inaccuracies or previously unidentified missing data were discovered the appropriate source documents or case report forms were consulted and corrections to the database were made as required. All corrections were logged so that changes could be audited. Accurate Community Health Index (CHI) numbers were required to ensure correct data linkage. These were checked by cross-checking them with dates of birth (the first 6 digits of CHIs correspond to individuals DOB). Several dates of birth were found to be inaccurate resulting in incorrect ages being calculated. All variables were summarised for maximum and minimum to identify significant outliers potentially due to typing errors (e.g. systolic BP 1300). The gender variable was cross-checked between the study database and the

screening log and also with the demographic data obtained via the data linkage to find cases where the gender had been miscoded.

2.6. Statistical analysis

Statistical analyses were performed using computer software (R 3.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS v 21 (IBM, New York, USA)). A 2-sided p value of <0.05 was taken to be significant for analyses. The statistical analysis plan was predetermined before data analyses.

2.6.1. Missing data

Missing data was quantified by ML in terms of number and percentage of data cases with missing data for each variable. Table 2.6 shows details of missing data from visit 1 data.

Where missing data accounted for less than 5% of the total cases missing data was treated as missing completely at random and the mean value for that variable was imputed. The only variable in the visit 1 data with 5% or more of cases missing was LDL cholesterol. This variable is calculated using the triglyceride, total cholesterol and HDL levels using the Friedewald equation. However if the triglyceride level is below the lower limit of the assay (0.51mmol/l) or above 4.51mmol/l the LDL level cannot be accurately estimated. The vast majority of cases of missing data for LDL were for this reason. Where the LDL measurement was missing cases were excluded from analyses.

Table 2.6: Summary of missing data of visit 1 variables

Variable	Number missing	% missing	How missing data dealt with/notes
Age	0	0	NA
Systolic BP	0	0	NA
Diastolic BP	0	0	NA
Heart rate	19	0.4	Mean value imputed
Total Cholesterol	1	<0.01	Mean value imputed
HDL cholesterol	2	<0.01	Mean value imputed
LDL cholesterol	323	7.3	Cases excluded from analysis
Triglycerides	3	0.1	Mean value imputed
Glucose	2391	54.1	Not included in analyses or summarised in this report*
ATPIII 10 year cardiovascular risk	9	0.2	Mean value imputed
ASSIGN score	44	1.0	Mean value imputed
Height	5	0.1	Mean value imputed
Waist circumference	27	0.6	Mean value imputed
Family history of CVD	0	0	NA
SIMD decile	11	0.2	
BNP	2	<0.01	Mean value imputed
Weight	4	0.1	Mean value imputed
Sex	0	0	NA
Smoking status	8	0.2	

BP=blood pressure, HDL=high density lipoprotein, LDL=low density lipoprotein, ATPIII= Adult Treatment Panel III, CVD=cardiovascular disease, SIMD=Scottish Index of Multiple deprivation, BNP= B-type natriuretic peptide. *Glucose measurement was only introduced after over half the study participants were recruited so over 50% have data missing. Therefore it has not been included in any analyses in this report.

2.6.2. Sample Size

The study aimed to recruit a total of 5000 subjects. Sub-division into the MRI group or BNP group was dependent upon the measured BNP level at the Visit 1.

The incidence of CV events was compared between the total MRI/BNP population and the BNP group. With 2 groups of 2500, one would have 80% power to distinguish rates of e.g. 2.7% v 1.5% ; RR= 1.8. The MRI/BNP groups were further divided into MRI/BNP_1 and MRI/BNP_2 depending on whether their BNP was above their gender specific 75^{th} percentile (i.e. splitting the MRI/BNP group in 2) to reflect those likely to have higher and lower left ventricular masses as per our hypothesis. In the 2 years follow-up we would expect the cumulative incidence in MRI/BNP_1 and MRI/BNP_2 to be 1.6% and 3.6% (8%/5 years and 18%/5 years). With 1250 in each group the power to detect this difference is 85%.

2.6.3. Baseline data analysis

Baseline cardiovascular risk factor, demographic and BNP data were summarised for the study population as a whole and for the BNP and MRI/BNP groups separately. The distributions of variables were assessed by plotting histograms of the variables. For normally distributed variables mean and standard deviation were calculated. For variables with a skewed distribution median and interquartile range were calculated. For categorical variables numbers and percentages were calculated. Differences in variables between BNP and MRI/BNP groups were compared using independent samples t-test for variables with a normal distribution Mann-Whitney tests for variables with a skewed distribution and chi square test for categorical variables. BNP results were calculated separately for men and women. Summaries of baseline characteristics were also calculated for gender specific quartiles of participants based on their BNP result. Differences in these variables between the top and bottom quartiles of BNP (gender specific) were assessed using independent samples t-tests for normally distributed variables, Mann-Whitney tests for variables with a skewed distribution and chi square test for categorical variables. Gender specific medians, 75^{th} and 90^{th} percentiles were calculated for age groups 40-44, 45-49, 50-54, 55-59, 60-64, 65-69 and 70+. Multivariable linear regression analyses were used to identify variables that were independently associated with BNP levels from among age, gender, smoking

status, systolic BP, diastolic BP, heart rate, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, BMI, waist circumference, family history of cardiovascular disease and SIMD decile. BNP was log10 transformed for this analysis to normalise its distribution.

The ASSIGN scores[41] were compared with the CHD risk scores calculated using the ATPIII guidelines[229] (that had been used to screen for eligibility for the study). The number and cardiovascular characteristics of those who would be reclassified using ASSIGN from low or intermediate risk to high risk were calculated. Similarly ASSIGN scores were calculated for those who failed screening for inclusion in the study based on a high predicted cardiovascular risk (using ATPIII). The number and characteristics of those who would be reclassified as intermediate or low risk and therefore may have been included in the study if ASSIGN score had been used to determine eligibility are presented. The mean difference between the ASSIGN and ATPIII scores for each individual was also calculated.

Descriptive demographic and cardiovascular risk statistics of the population who underwent MRI scans were calculated and presented as means and standard deviations for variables with a normal distribution, medians and interquartile ranges for those with a skewed distribution and as frequencies and percentages for those with categorical outcomes. Left ventricular measures were summarised for men and women separately. The nature of the distribution of the left ventricular variables was assessed by plotting histograms of the variables. Left ventricular mass was indexed using a variety of methods reported in the literature (by dividing by height, $height^{1.7}$, $height^{2.7}$, body surface area calculated using the Dubois formula[235] and body surface area calculated using the Mosteller formula[236]). Differences in the measures between the 2 genders were compared using independent samples t-tests. Correlations between BNP and LV measures were assessed using Spearman rank correlation tests. Mean LV parameters were compared between those with BNP levels above and below

gender specific 75th, 90th and 95th percentiles using independent samples t-tests. Gender specific univariate analyses of baseline cardiovascular and demographic risk factors with LV results were performed using Spearman rank correlations. Multivariable linear regression analysis was performed to identify variables that were associated with the various LV measures. The models included age, systolic BP, diastolic BP, heart rate, HDL cholesterol, LDL cholesterol, triglycerides, BMI, waist circumference, smoking status, family history of CVD, SIMD decile and BNP. Age, heart rate, triglycerides, BMI and BNP were log transformed to normalise the distribution of the variables as were all the left ventricular measures except stroke volume (which already had a normal distribution).

Standardised atheroma scores (SAS) derived from the whole body angiography were presented as medians, 80th percentile and 90th percentile as the variable was very strongly positively skewed. Total population and gender specific univariate analyses were performed using Spearman rank correlation to investigate associations between SAS and baseline cardiovascular risk factors and BNP, and between the percentage of arterial segments with any stenosis and baseline cardiovascular risk factors and BNP. Multivariable linear regression analysis was performed to identify variables that predicted the SAS. The initial model included age, gender, smoking status, systolic BP, diastolic BP, heart rate, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, BMI, waist circumference, family history of cardiovascular disease, SIMD decile and BNP level. Differences in baseline variables were compared between those with SAS below and above 80th percentile and between those with any arterial stenosis and those with none (SAS = 0 v. SAS >0). Independent samples t-test was used for variables with a normal distribution and Mann-Whitney test for variables with a skewed distribution. Correlations between LV measures and SAS and between LV measures and percentage of arterial segments with any stenosis were analysed using Spearman rank correlation. Mean left ventricular measurements were compared between those with an SAS greater and less than the gender specific 80th percentile and between

those with and without any arterial stenosis (SAS = 0 v. SAS>0) using independent samples t tests.

2.6.4. Screen fail population

Baseline data

Baseline cardiovascular risk factor, demographic and BNP data were summarised for the participants who failed screening due to predicted cardiovascular risk ≥20% or hypertension. Figures were calculated separately for the 2 groups (hypertension and high CV risk). For normally distributed variables mean and standard deviation were calculated. For variables with a skewed distribution median and interquartile range were calculated. For categorical variables numbers and percentages were calculated.

Prescribing data

Those who failed screening due to either hypertension, high CV risk or dyslipidaemia and who had been prescribed a cardiovascular drug of interest indicated by the BNF codes described earlier in section 2.4.2 were identified. Minimum, maximum, and quartiles of time since last prescription until time of screening was calculated for the population as a whole and for the hypertensive and high cardiovascular risk groups separately.

For participants who failed screening due to hypertension, high CHD risk or dyslipidaemia and who had not received a prescription of interest in the 6 months prior to screening (to exclude those who were already on or had recently received drugs of interest) take up rates of post-screening cardiovascular drugs of interest were calculated, with each person's follow-up time calculated from screening date to earliest of first drug of interest prescription, death or end of study date. Rates of prescription were calculated per 1000 patient years at risk. For analysis of time to first prescription, Kaplan Meier analysis was performed comparing time to first prescription between those who failed screening due to hypertension and high cardiovascular risk.

The effect of CV medication prescription on event rates in those who had failed screening due to hypertension, high CHD risk or dyslipidaemia and who had not received a prescription of interest in the 6 months prior to screening was investigated. Each person's follow up was split into 56 day intervals. At the start of each interval binary exposure statuses were recorded (1 if prescription issued in previous 56 days, 0 otherwise), along with current age. A time-updated Cox proportional hazard survival model including current exposure status, current age and sex was used to assess the effect of current exposure on CV event hazard.

2.6.5. Assessment of Outcomes

Participants in the MRI/BNP Group were withdrawn (censored) from the time to event analysis once they had experienced a cardiovascular event or procedure indicated by the ICD10 or OPCS4 codes described earlier in section 2.4.2. If ICD10 or OPCS4 codes belonged to the specified codes and the date was after the recruitment date, the time to event or hospital admission was calculated as the difference between admission date and recruitment date. Where a subject had no events/admissions, time at risk was calculated as the difference between the date the participant was last known to be alive and recruitment date. For analysis of time to first admission, life table analysis was used, by 1-year intervals. From GRO death data, we determined the date of death where available. Survival time in days was calculated by subtracting the recruitment date from date of death. For subjects still alive, the time of follow-up was found from the time between recruitment and date of latest update or date withdrawn from study, whichever was earlier.

Time to first admission for any of the ICD/OPCS ranges or death were calculated (primary outcome). It was planned to analyse separately for outcomes of MI, angina, stroke and sudden death but at the early stage of follow up reported in this thesis only a very small number of events had occurred so this sub analysis has not been

performed. It is planned to do this for further follow up analyses in the future when more events are expected to occur.

Cumulative incidence of events and death was compared between BNP groups, with 95% CI. Relative risk (hazard ratio) with 95% CI for high versus low BNP were calculated from a Cox regression model.

It was planned to analyse incidence rates of death at follow up using life table analysis of all-cause mortality by BNP level (high versus low) to determine cumulative mortality rates at 2 years. Death from MI, angina, stroke and sudden death were to be analysed separately. However at the stage of follow up reported in these thesis (mean follow up per participant 4.03 and 4.33 years for BNP and MRI/BNP groups respectively) only 2 deaths had occurred so this analysis was not performed. It is planned to do this for further follow up analyses at 5, 10, 15 and 20 years.

Event rates and 95% confidence intervals (combined death and cardiovascular events) were calculated for those with LVM, LVMIs (using each of the indexing methods) in the top and bottom quartiles for their gender. The difference in rates were deemed as significant if the CIs did not overlap.

3. Results part 1 – study participants

3.1. Recruitment and eligibility

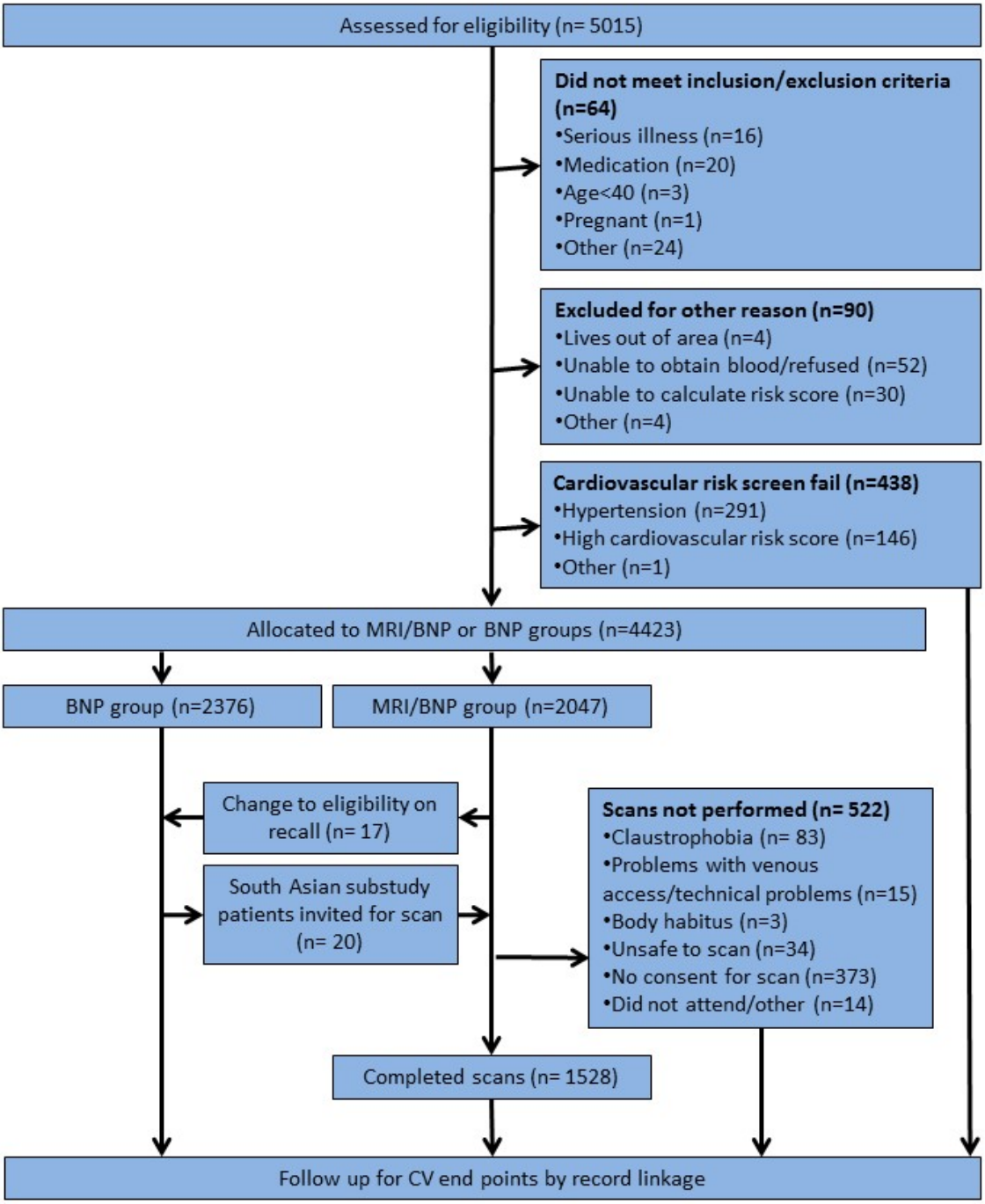
5015 people attended the CRC at Ninewells Hospital (n=2066, 41.2% male) for screening between 26th November 2007 and 6th February 2013. 64 (n=21, 32.8% male) were found not to meet the inclusion or met exclusion criteria for a variety of reasons shown in the figure. A further 90 people (n=34, 37.8% male) were excluded as either they lived outside the recruitment area (n=4, all male) or it was not possible to calculate a cardiovascular risk score because either blood was not obtained (n=52, 9 male), the sample could not be analysed or HDL too low or high for the algorithm to calculate the score (n=30, 21 male).

291 (137 47.1% male) were failed at the screening phase due to hypertension, defined as a BP >145/90mmHg. A further 146 (142, 97.3% men) were then excluded due to a predicted cardiovascular risk score ≥20% and 1 (woman) was excluded due to marked dyslipidaemia. The characteristics of those who failed screening are described in section 3.2.

4423 (1740, 39.3% male) participants were therefore eligible to be allocated to either the BNP or BNP/MRI groups depending on their BNP result.

The CONSORT diagram (figure 3.1) summarises the flow of participants through the TASCFORCE study including those who were excluded at the screening visit.

Figure 3.1 CONSORT diagram showing participant flow through study



MRI=magnetic resonance imaging, BNP=B-type natriuretic peptide, CV=cardiovascular

3.2. Cardiovascular risk incidental findings

438 participants (8.7% of those screened) were found to have either an estimated 10 year cardiovascular risk of >20%, hypertension or dyslipidaemia requiring treatment under current guidelines. The characteristics of these groups of participants are summarised in table 3.1.

Table 3.1: Characteristics of subjects excluded due to presence of cardiovascular risk (characteristics of the eligible population are included for comparison)

Variable		Screen fail population: Hypertensive (BP> 145/90 mmHg) (n=291)	Screen fail population: 10 year CHD risk ≥20% (n=146)	Eligible population (n=4423)
Median (IQR) age (years)		58.2 (12.2)	58.7 (15.2)	51.2 (11.8)
No (%) men		138 (47.4)	142 (97.3)	1740 (39.3)
No (%) current smokers		34 (11.7)	85 (58.2)	572 (12.9)
No (%) former smokers		65 (22.3)	24 (16.4)	1226 (27.7)
No (%) never smokers		151 (51.9) *(N/A41)*	37 (25.3)	2617 (59.2)
Mean (SD) systolic BP(mmHg)		156.5 (9.8)	132.2 (10.9)	122.4 (11.9)
Mean (SD) diastolic BP(mmHg)		88.9 (9.7)	77.3 (9.5)	73.4 (9.3)
Medan (IQR) heart rate (beats per min)		72 (16) (*N/A215)*	68 (14) *(N/A11)*	65 (12)
Mean (SD) total cholesterol (mmol/L)		5.69 (1.03) *(N/A55)*	6.07 (1.02)	5.48 (1.00)
Mean (SD) high density lipoprotein (mmol/l)		1.42 (0.48) *(N/A58)*	0.89 (0.24)	1.38 (0.43)
Mean (SD) low density lipoprotein (mmol/l)		3.34 (0.92) *(N/A71)*	3.93 (0.93) *(N/A17)*	3.40 (0.90)
Median (IQR) triglycerides (mmol/l)		1.82 (1.38) *(N/A55)*	2.50 (1.93)	1.34 (1.09)
Median (IQR) Body mass index (kg/m^2)		27.5 (5.5) *(N/A202)*	28.3 (4.7) *(N/A6)*	26.5 (5.58)
Median (IQR) weight (kg)		82.0 (18.6) *(N/A202)*	83.6 (17.3) *(N/A6)*	74.7 (20.7)
Mean (SD) height (cm)		168.5 (8.2) *(N/A202)*	173.4 (7.5) *(N/A6)*	167.4 (9.2)
Mean (SD) waist circumference (cm)		91.1 (13.4) *(N/A216)*	97.0 (12.9) *(N/A10)*	87.5 (13.3)
Median (IQR) 10 year CHD event risk estimation (%)		5.0 (9.0) *(N/A72)*	20.0 (5.0)	2.0 (5.0)
No (%) with family history of CVD		49 (16.8) *(N/A96)*	35 (23.2) *(N/A9)*	1075 (24.3)
SIMD Number (%)	1	12 (4.1)	8 (5.5)	217 (4.9)
	2	19 (6.5)	11 (7.5)	251 (5.7)
	3	29 (10.0)	20 (13.7)	357 (8.1)
	4	19 (6.5)	10 (6.8)	250 (5.7)
	5	14 (4.8)	10 (6.8)	269 (6.1)
	6	21 (7.2)	14 (9.6)	424 (9.6)
	7	45 (15.5)	22 (15.1)	683 (15.4)
	8	51 (17.5)	22 (15.1)	843 (19.1)
	9	61 (21.0)	24 (16.4)	799 (18.1)
	10	18 (6.2)	4 (2.7)	319 (7.2)
	N/A	*2 (0.7)*	1 (0.7)	11 (0.2)

Mean and standard deviation are given for variables with a normal distribution and median and interquartile range for those with a skewed distribution. SD=standard deviation. IQR=interquartile range. BP=blood pressure. CHD=coronary heart disease, CVD=cardiovascular disease, SIMD=Scottish Index of Multiple Deprivation. Full data was not collected for all screen-failed participants: the number of participants with missing data is indicated in italics. Only one subject was excluded due to dyslipidaemia so summary figures are not given for this person. N/A=not available.

3.3. Baseline characteristics of eligible participants

3.3.1. Demographics and baseline cardiovascular risk factors

4423 participants were eligible to enter the main part of the study. 2376 people (937 male) were allocated to the BNP group and 2047 (803 male) were allocated to the MRI/BNP group based on their BNP result. The characteristics of the participants in each of these groups and the eligible population as a whole are summarised in table 3.2. Compared to the BNP group the MRI/BNP group was older, contained less current smokers and more never smokers, had a slightly higher systolic blood pressure, lower resting heart rate, higher high density lipoprotein (HDL), lower triglycerides, slightly lower BMI and lower waist circumference. They had a higher predicted risk using both the ATPIII and ASSIGN algorithms and contained more people with an intermediate predicted risk (10-19.9%).

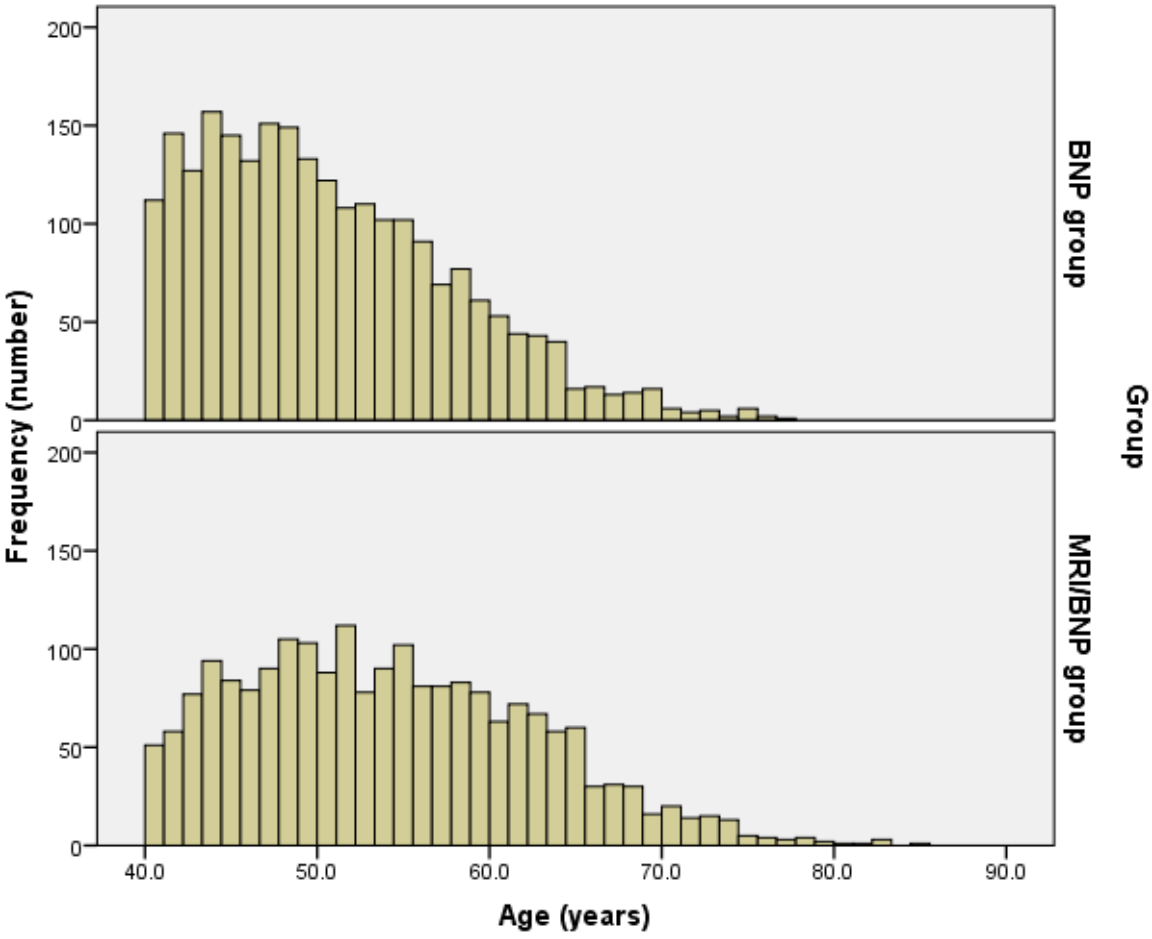
The distribution of age is illustrated in figure 3.2. The distribution of CHD risk scores for the BNP and the MRI/BNP populations are illustrated in figure 3.3. Both these distributions were positively skewed.

Table 3.2: Baseline characteristics of participants eligible for the TASCFORCE study

Baseline characteristics		Eligible population (n=4423)	BNP group (n=2376)	MRI/BNP group (n=2047)	Difference between BNP and MRI/BNP groups*
Median (IQR) age (years)		51.2 (11.8)	49.5 (10.6)	53.4 (12.5)	**p<0.001**
No (%) men		1740 (39.3)	937 (39.4)	803 (39.3)	p=0.94
No (%) current smokers		572 (12.9)	351 (14.8)	221 (10.8)	**p<0.001**
No (%) former smokers		1226 (27.7)	663 (27.9)	563 (27.5)	p=0.81
No (%) never smokers		2617 (59.2)	1361 (57.3)	1256 (61.4)	**p=0.004**
Mean (SD) systolic BP(mmHg)		122.4 (11.9)	122.1 (11.7)	122.9 (12.0)	**p=0.027**
Mean (SD) diastolic BP(mmHg)		73.4 (9.3)	73.6 (9.4)	73.1 (9.2)	p=0.06
Median (IQR) heart rate (bpm)		65 (12)	67 (14)	63 (12)	**p<0.001**
Mean (SD) total cholesterol (mmol/L)		5.48 (1.00)	5.47 (1.02)	5.48 (0.99)	p=0.79
Mean (SD) high density lipoprotein (mmol/l)		1.38 (0.43)	1.34 (0.44)	1.43 (0.42)	**p<0.001**
Mean (SD) low density lipoprotein (mmol/l)		3.40 (0.90)	3.41 (0.92)	3.40 (0.42)	p=0.84
Median (IQR) triglycerides (mmol/l)		1.34 (1.09)	1.38 (1.18)	1.29 (1.02)	**p<0.001**
Median (IQR) body mass index (kg/m^2)		26.5 (5.6)	26.7 (5.8)	26.2 (5.4)	**p<0.001**
Median (IQR) weight (kg)		74.7 (20.7)	75.0 (21.2)	74.1 (20.0)	p=0.08
Mean (SD) height (cm)		167.4 (9.2)	167.1 (9.1)	167.7 (9.3)	**p=0.041**
Mean (SD) waist circumference (cm)		87.5 (13.3)	88.0 (13.6)	86.9 (13.0)	**p=0.006**
Median (IQR) 10 year CHD event risk estimation using ATPIII algorithm (%)		2.0 (5.0)	2.0 (5.0)	2.0 (5.0)↑	**p<0.001**
Median (IQR) 10 year cardiovascular event estimation using ASSIGN algorithm (%)		7.0 (7.3)	6.6 (6.7)	7.6 (6.7)	**p<0.001**
No (%) with 10 year CHD risk 10-19.9% (using ATPIII algorithm)		602 (13.6)	286 (12.0)	316 (15.4)	**p=0.001**
No (%) with family history of CV disease		1075 (24.3)	561 (23.6)	514 (25.1)	p=0.25
SIMD Number (%)	1	217 (4.9)	132 (5.6)	85 (4.2)	p=0.054
	2	251 (5.7)	145 (6.1)	106 (5.2)	
	3	357 (8.1)	208 (8.8)	149 (7.3)	
	4	250 (5.7)	134 (5.6)	116 (5.7)	
	5	269 (6.1)	143 (6.0)	126 (6.2)	
	6	424 (9.6)	218 (9.2)	206 (10.1)	
	7	683 (15.4)	349 (14.7)	334 (16.3)	
	8	843 (19.1)	442 (18.6)	401 (19.6)	
	9	799 (18.1)	428 (18.0)	371 (18.1)	
	10	319 (7.2)	169 (7.1)	150 (7.3)	
	N/A	11 (0.2)	8 (0.3)	3 (0.1)	-

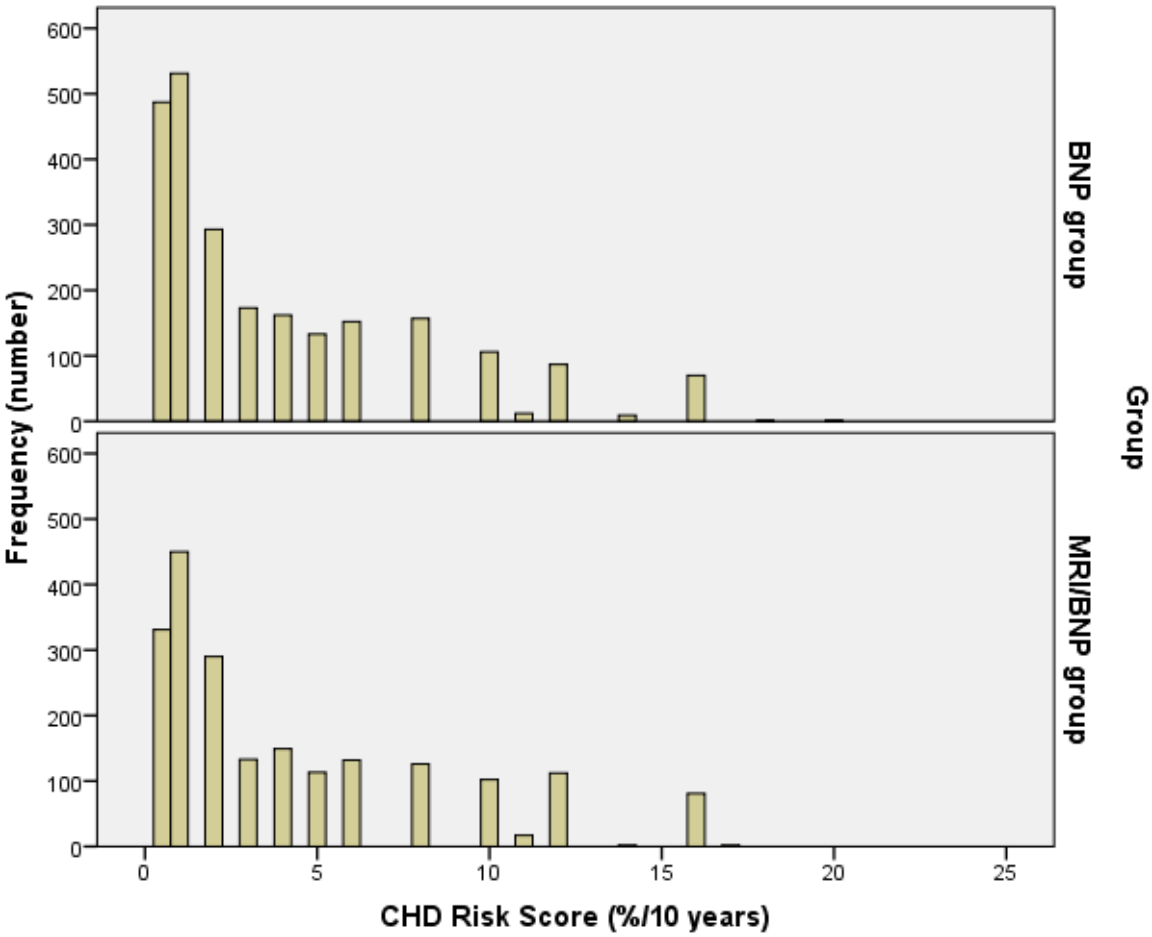
[Notes for table 3.2]
IQR=inter-quartile range, SD=standard deviation, SIMD = Scottish Index of Multiple Deprivation, ATPIII=Adult Treatment Panel III.
For variables with a normal distribution mean and standard deviation are given. For those with a skewed distribution median and interquartile range are given. *Comparisons for continuous variables with normal distributions are independent samples unpaired t-tests and for skewed distribution and ranked scores (i.e. SIMD) the Wilcoxan Mann-Whitney test. Chi-square tests were used for binomial variables.

Figure 3.2: Distribution of age in the eligible population



BNP = B-type natriuretic peptide. BNP group = those with BNP less than their gender median. MRI/BNP group = those with BNP less than their gender median. Frequency scale is number of participants.

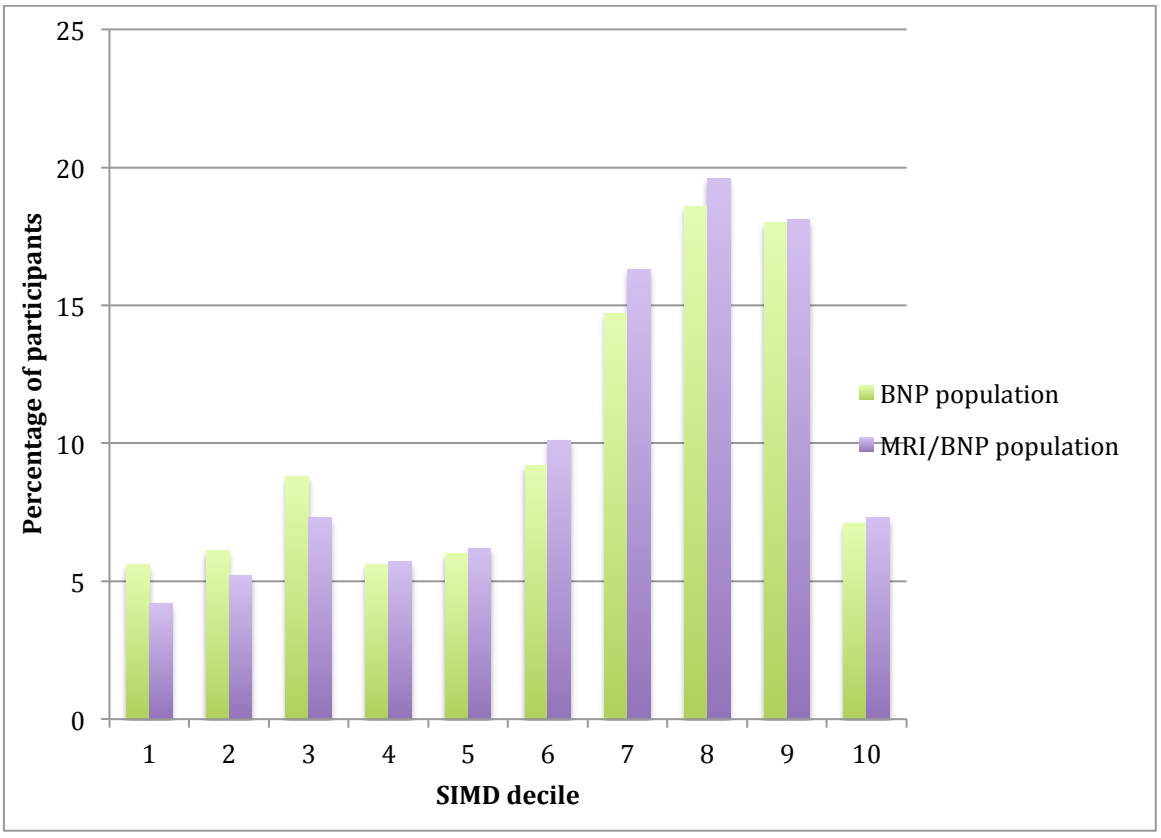
Figure 3.3: Distribution of CHD risk scores calculated using ATPIII algorithm in the BNP and MRI/BNP populations



BNP=B-type natriuretic peptide. BNP group=those with BNP less than their gender median. MRI/BNP group=those with BNP less than their gender median. Frequency scale is number of participants.

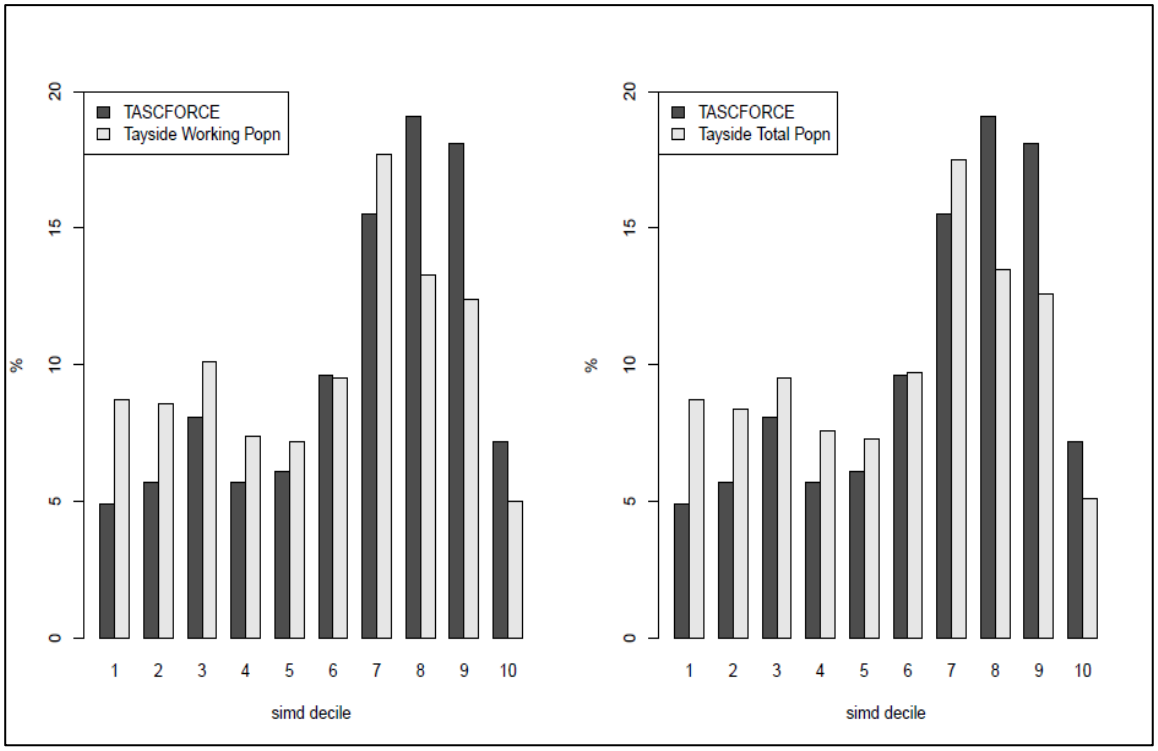
The spread of participants from deciles of the Scottish Index of Multiple Deprivation (SIMD) is illustrated in figure 3.4. The distribution of TASCFORCE participants by SIMD decile is compared with the Tayside entire and working populations in figure 3.5. Those from areas of less deprivation were slightly overrepresented compared to those from areas of greater deprivation. The distributions of SIMD deciles were similar for both the BNP and MRI/BNP groups.

Figure 3.4: Spread of Scottish Index of Multiple Deprivation (SIMD) scores in eligible population



Lower deciles of SIMD indicate living in an area of increased multiple deprivation.

Figure 3.5: Distribution of TASCFORCE participants by SIMD decile compared with Tayside working population (left) and Tayside total population (right)



Tayside population data from 2006 SIMD data for Dundee City, Angus and Perth and Kinross local authority areas.[237] Lower deciles of SIMD indicate living in an area of increased multiple deprivation. SIMD = Scottish Index of Multiple Deprivation.

4282 (1685 men) consented to having their blood samples retained to enter the genetic substudy. It is planned to genotype these samples to look for genetic variations that may be associated with cardiovascular disease.

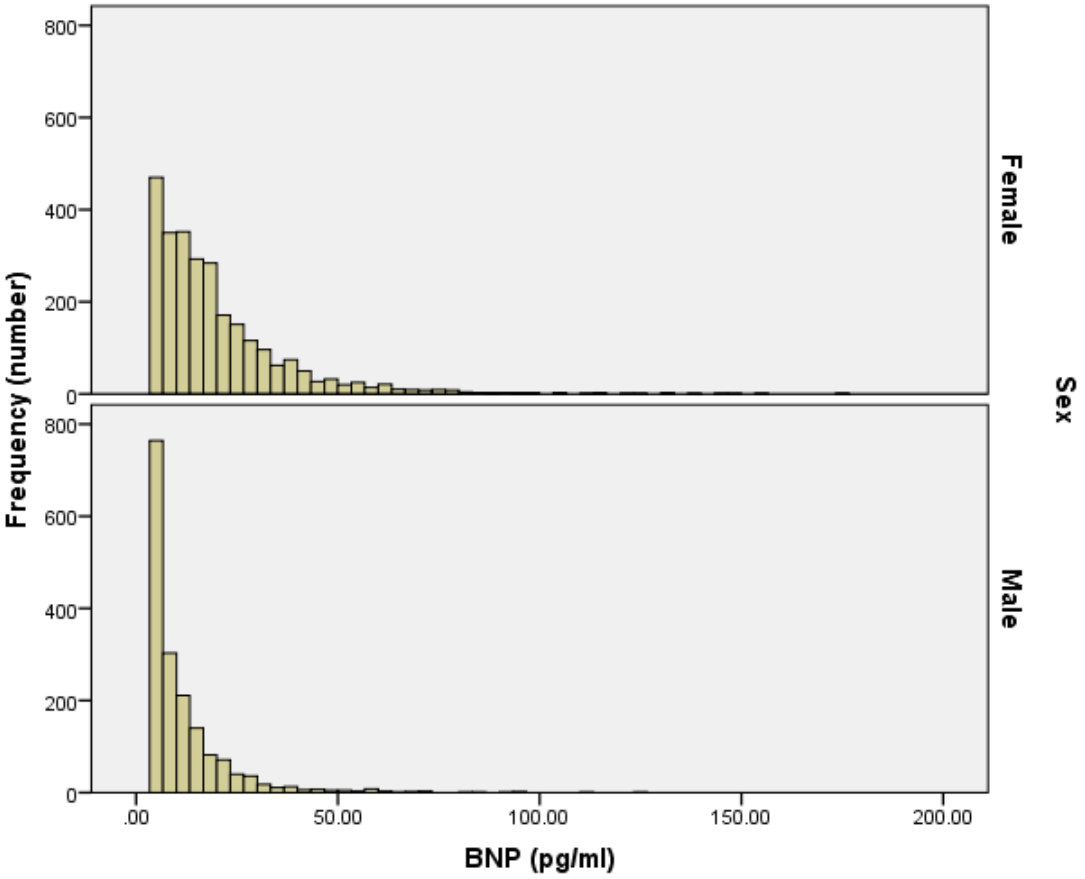
3.3.2. BNP results

The B-type natriuretic peptide (BNP) results for eligible participants are summarised in table 3.3. The distribution of BNP results is illustrated in the histograms (figure 3.6). The median BNP results were higher for women compared to men. For comparison the cut off BNP value for allocating participants to the BNP or MRI/BNP groups (the gender specific median after recruitment of 2000 people) is given to allow comparison of the final study population with this cut off. BNP results were strongly positively skewed for both men and women.

Table 3.3: B-type natriuretic peptide (BNP) results for eligible participants

	Median (IQR) pg/ml	Cut off used for BNP v. MRI/BNP allocation
All eligible participants	11.8 (14.6)	N/A
Men	7.5 (8.9)	8.2
Women	15.3 (16.7)	16.4

Figure 3.6: Distribution of BNP results for men and women



Values below the detection limit (5.0pg/ml) are reported as 4.9pg/ml. Frequency scale is number of participants.

BNP results for men and women were compared using a Mann-Whitney test and demonstrated a significant difference for the results between the genders ($p<0.001$). Because the BNP results were positively skewed and mostly within a "normal" clinical range (e.g. below that for diagnosing heart failure) the values for 50^{th}, 75^{th}, 90^{th}, 95^{th}, 97.5^{th} and 99^{th} percentiles have been calculated for each gender and are summarised in table 3.4.

Table 3.4: Percentiles of BNP results for each gender

	Median	75th percentile	90th percentile	95th percentile	97.5th percentile	99th percentile
Men	7.50	13.80	23.10	30.60	44.30	59.72
Women	15.30	25.30	39.40	53.36	65.16	83.19

3.3.3. Comparison of estimated cardiovascular risk using ASSIGN and ATPIII algorithms

The study used the ATPIII algorithm for deriving the predicted cardiovascular risk score however now local guidelines in Tayside advise the use of the ASSIGN risk score, which has been derived from a Scottish population. Therefore differences in the scores obtained for each participant using the two different scores were analysed. Table 3.5 summarises the differences between the two risk prediction tools.

Table 3.5: Differences between ATPIII and ASSIGN scores

Scoring system	End points	Time point (years)	Variables included
ASSIGN[41]	• Death from cardiovascular causes • Coronary heart disease • Cerebrovascular disease • Coronary artery interventions	10	• Age • Gender • Family history of coronary heart disease/stroke • Diabetes • Rheumatoid arthritis • Smoking habit • Systolic blood pressure • Total cholesterol • High density lipoprotein • Social deprivation
Adult Treatment Panel III[229]	• Acute myocardial infarction • Coronary heart death (sudden or not)	10	• Age • Gender • Systolic BP • Treatment for hypertension • Total cholesterol • High density lipoprotein • Smoking

Effect on reclassification

The study population, including those who failed screening due to high predicted cardiovascular risk, were categorised according to their estimated 10 year cardiovascular risk: <10% were classified as low risk, 10-19.9% intermediate risk and ≥20% as high risk. Using the ASSIGN score resulted in the reclassification of 1105 (24.7%) of participants with both ATPIII and ASSIGN scores available. Of these 992 (22.1%) were “up-classified” to a higher risk category and 113 (2.5%) were “down-classified”. Table 3.6 shows the breakdown of reclassification.

Table 3.6: Reclassification of risk categories using the ASSIGN score instead of the ATPIII derived score (percentages reflect those reclassified from the given ATPIII derived category)

Risk Category using ATPIII algorithm	Risk category using ASSIGN score		
	Low risk (<10%)	Intermediate risk (10-19.9%)	High risk (≥20%)
Low risk (<10%)	-	734 (19.3%)	109 (2.9%)
Intermediate risk (10-19.9%)	61 (10.1%)	-	149 (24.8%)
High risk (≥20%)	5 (3.4%)	47 (32.2%)	-

53 (36.3%) of participants found to be ineligible for the study due to a high ATPIII derived CHD risk score had an ASSIGN score <20 indicating that they may have been eligible for the study if this score had been used to determine eligibility. Those with an ASSIGN score less than 20 had a mean age of 51.9 years (SD 5.48), mean systolic BP of 125.7 mmHg (SD 11.10), mean diastolic BP 75.8 mmHg (SD 9.74), mean heart rate 58.6 beats per minute (SD 40.6), mean total cholesterol 6.14 mmol/l (SD 0.98), mean HDL 0.90 mmol/l (SD 0.26), mean LDL 3.92 mmol/l (SD 0.91), median triglycerides

2.77 mmol/l (IQR 2) and median BMI 28.4 kg/m^2 (IQR 5). 50 (94.3%) were male, 4 (7.5%) were never smokers, 1 (1.9%) was an ex-smoker, 48 (90.6%) were current smokers and 10 (18.9%) had a family history of CV disease.

258 (5.8%) participants found to be eligible for the study based on their ATPIII score had an ASSIGN score ≥20 (indicating a 10 year cardiovascular risk of ≥20% using the ASSIGN algorithm). Those with an ASSIGN score ≥20 had a mean age of 66.4 years (SD 9.66), mean systolic BP 130.7 mmHg (SD 9.53), mean diastolic BP 75.1 (SD 8.84), mean heart rate 66.3 bpm (SD 9.66), mean total cholesterol 6.02 mmol/l (SD 1.04), mean HDL 1.21 mmol/l (SD 0.40), mean LDL 3.88 mmol/l (SD 0.96), median triglycerides (1.83 mmol/l (IQR 1.33) and median BMI 27.0 kg/m^2 (IQR 5.38). 140 (54.3%) were male, 114 (44.2%) were never smokers, 98 (38.0%) were ex-smokers, 46 (17.8%) were current smokers and 100 (38.8%) had a family history of CV disease. These characteristics and the distribution by SIMD deciles are summarised in table 3.7.

Table 3.7: Characteristics of participants with ASSIGN score ≥20. The figures for the entire eligible population (including those with ASSIGN score ≥20) are given for comparison

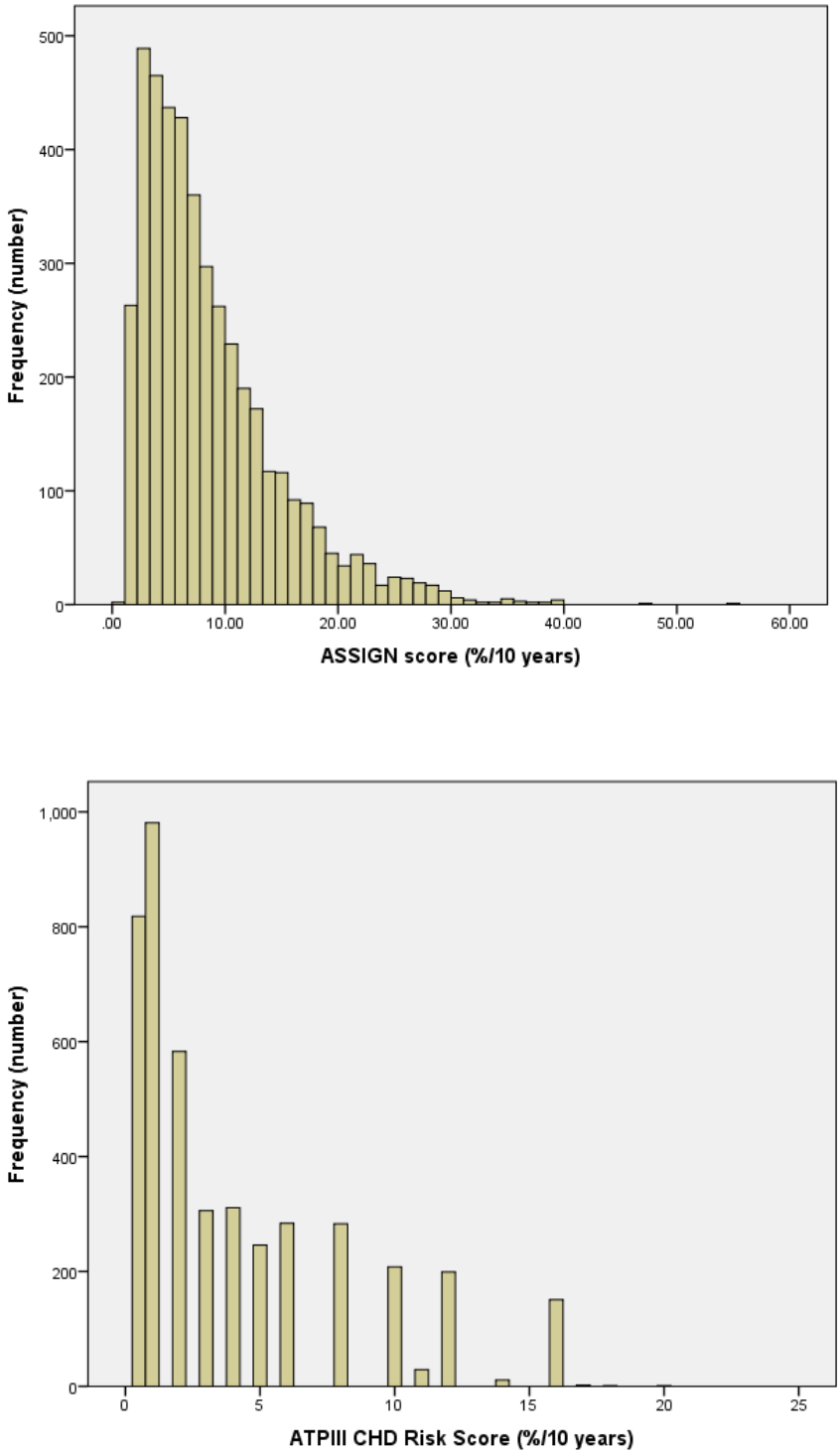
Baseline characteristics		ASSIGN score ≥20 (n=258)
Median (IQR) age (years)		66.4 (9.4)
No (%) men		140 (54.3)
No (%) current smokers		46 (17.8)
No (%) former smokers		98 (38.0)
No (%) never smokers		114 (44.2)
Mean (SD) systolic BP(mmHg)		130.7 (9.5)
Mean (SD) diastolic BP(mmHg)		75.1 (8.8)
Median (IQR) heart rate beats per min		65 (14)
Mean (SD) total serum cholesterol (mmol/L)		6.02 (1.04)
Mean (SD) high density lipoprotein (mmol/l)		1.21 (0.40)
Mean (SD) low density lipoprotein (mmol/l)		3.88 (0.96)
Median (IQR) triglycerides (mmol/l)		1.83 (1.33)
Median (IQR) body mass index		27.0 (5.4)
No (%) with family history of CV disease		100 (38.8)
Scottish Index of multiple deprivation (SIMD) Number (%)	1	19 (7.4)
	2	23 (9.9)
	3	32 (12.4)
	4	18 (7.0)
	5	14 (5.4)
	6	24 (9.3)
	7	36 (14.0)
	8	44 (17.1)
	9	35 (13.6)
	10	13 (5.0)
	N/A	0 (0.0)

BP= Blood pressure, IQR=interquartile range, SD=standard deviation,CV=cardiovascular, N/A= data not available (number indicates number of participants with no data).

Eligible population

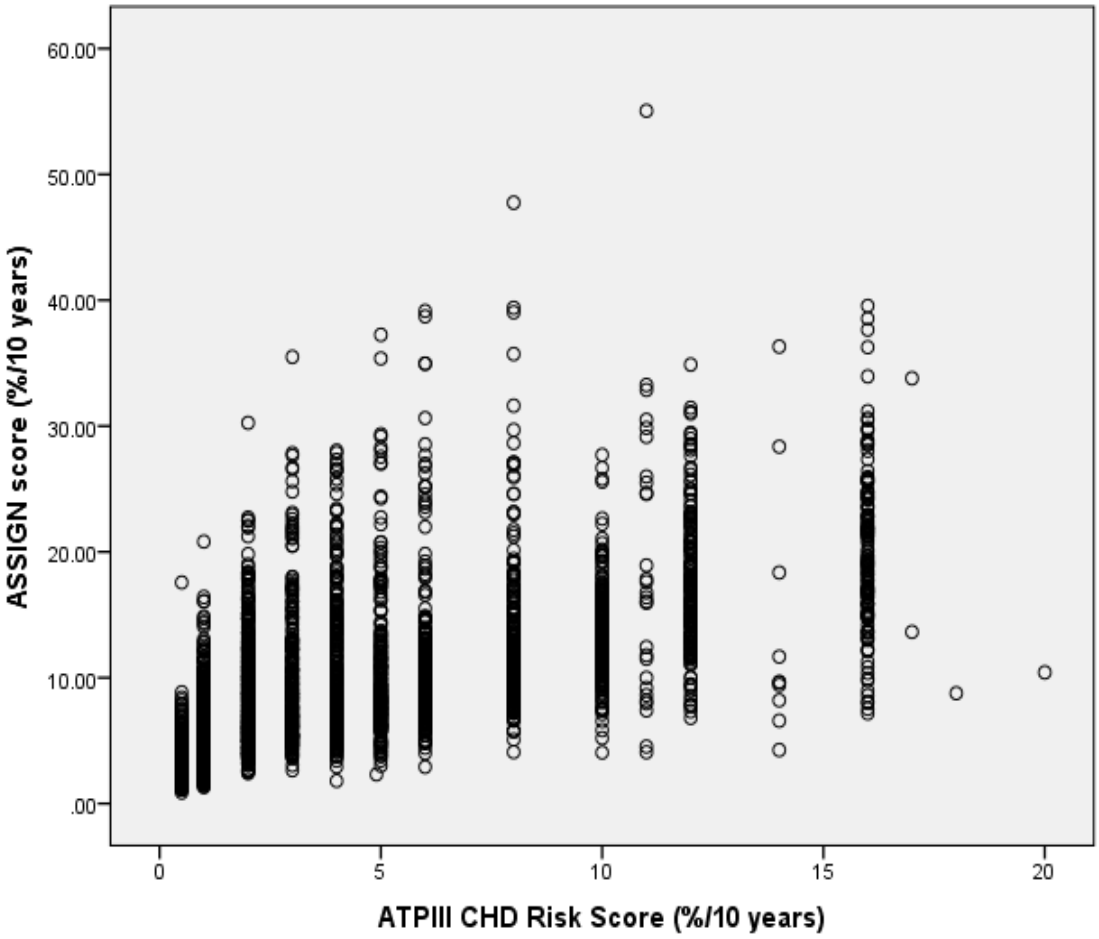
The distribution of estimated 10-year cardiovascular risk using both the ATP III guidelines and the ASSIGN score for those participants eligible to enter the study are illustrated in figure 3.7. The distributions of both of the scores were positively skewed.

Figure 3.7: Distributions of ASSIGN risk scores (top) and risk score estimated using ATPIII algorithm (bottom) for all participants eligible to enter the TASCFORCE study



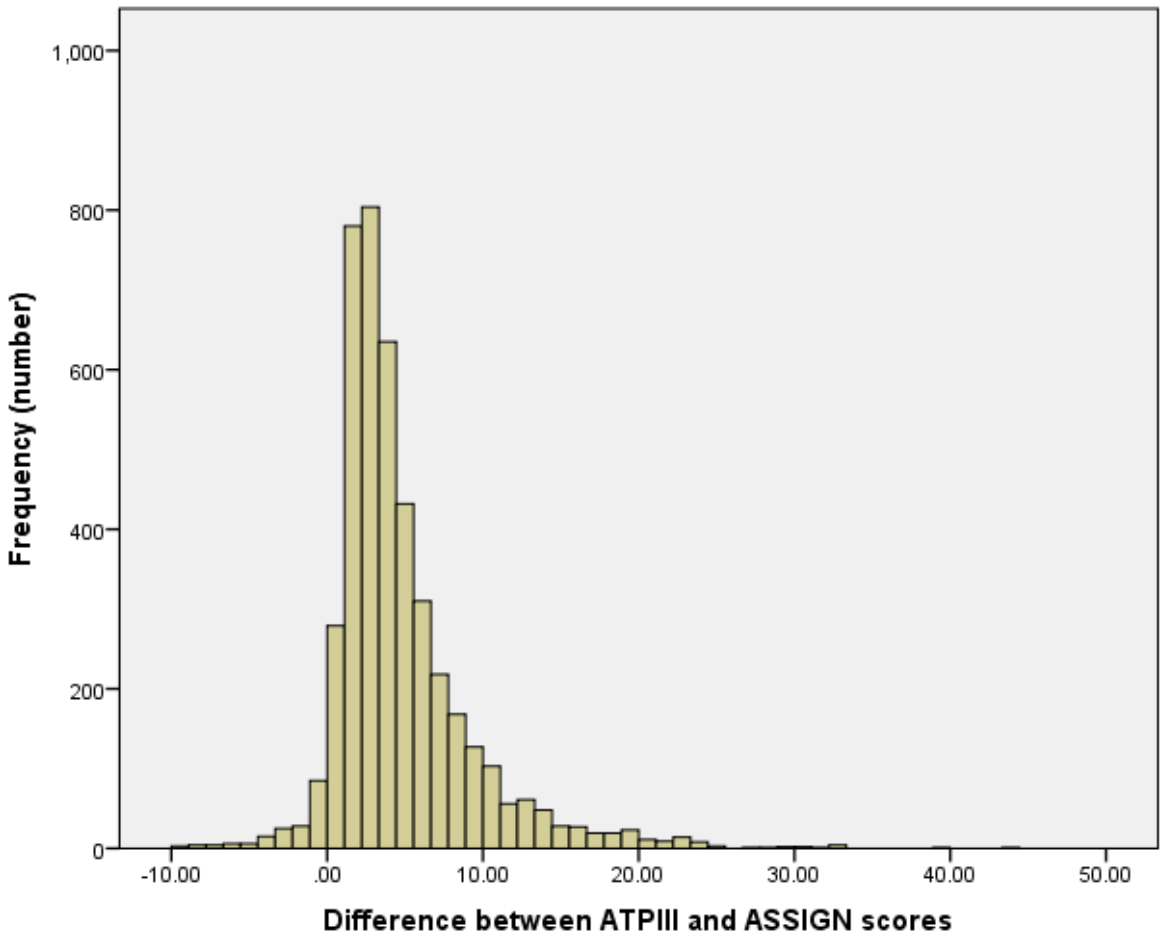
The correlation between the ATPIII risk score and ASSIGN score is shown in figure 3.8. Using a Spearman rank correlation test the correlation between the 2 scores was very good ($\rho=0.796$, $p<0.001$).

Figure 3.8: Correlation between ASSIGN and ATPIII risk scores



The difference between the predicted risk scores calculated using the ATPIII algorithm and those calculated using the ASSIGN algorithm is illustrated in figure 3.9. The mean difference between the scores was 4.72 with a maximum of 44.1 (a positive result indicating ASSIGN score greater than ATPIII score) and minimum -9.7 (a negative result indicating ASSIGN score less than ATPIII score). Most people had an ASSIGN score greater than their ATPIII score.

Figure 3.9: Distribution of difference between ATPIII derived CHD risk score and ASSIGN derived CV risk score for participants eligible to enter the TASCFORCE study based on their ATPIII score



Difference calculated by subtracting ATPIII score from ASSIGN score for each participant.

Potential participants who failed screening due to high cardiovascular risk

The distribution of ASSIGN scores for those found to be ineligible for the TASCFORCE study at screening because of a high predicted CHD risk (using ATPIII guidelines) is illustrated in figure 3.10. The distribution of difference between ATPIII derived score and ASSIGN score is illustrated in figure 3.11. The mean difference between ATPIII derived score and ASSIGN score in this group was 2.23 (SD 10.34). As with the eligible population more people had an ASSIGN score that was greater than their ATPIII score.

Figure 3.10: Distribution of ASSIGN scores in participants ineligible to enter TASCFORCE study due to high predicted cardiovascular risk using ATPIII guidelines

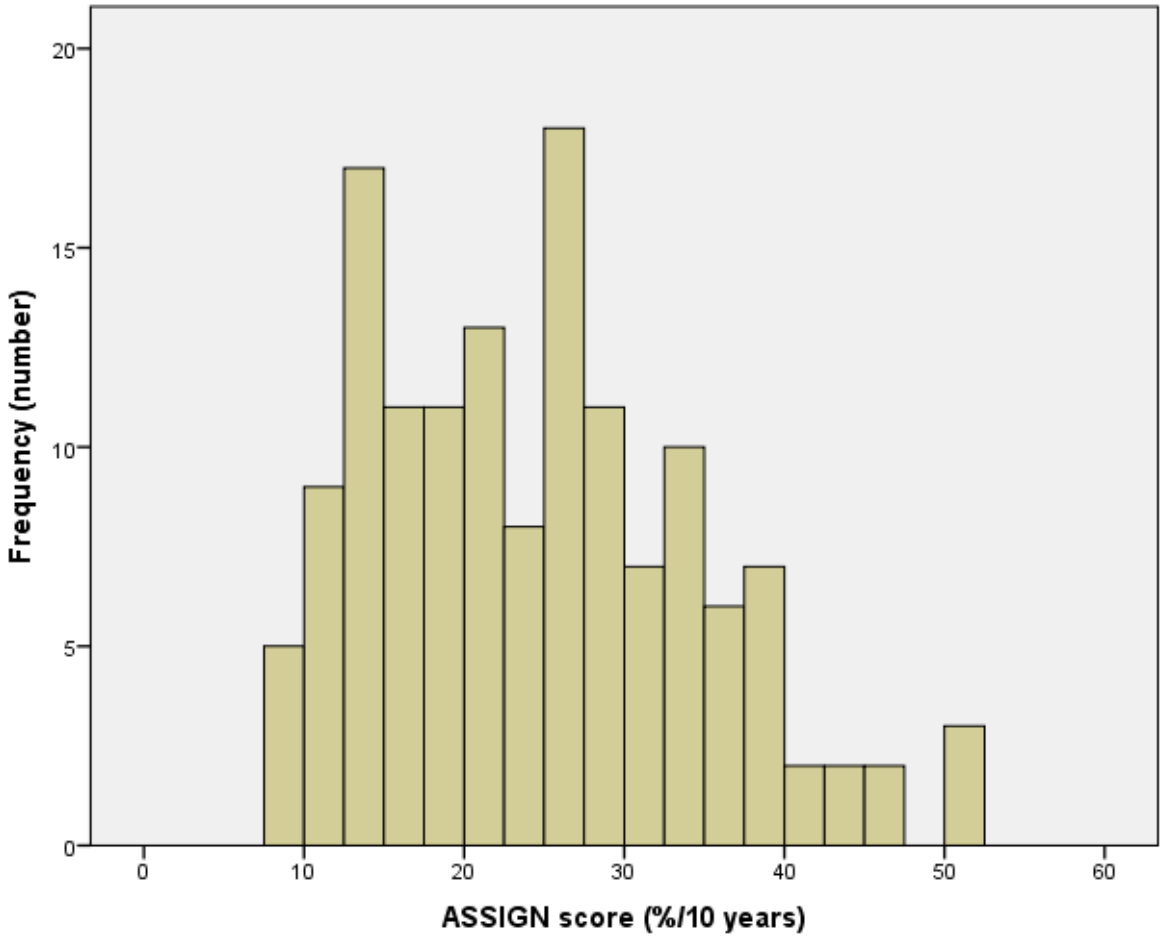
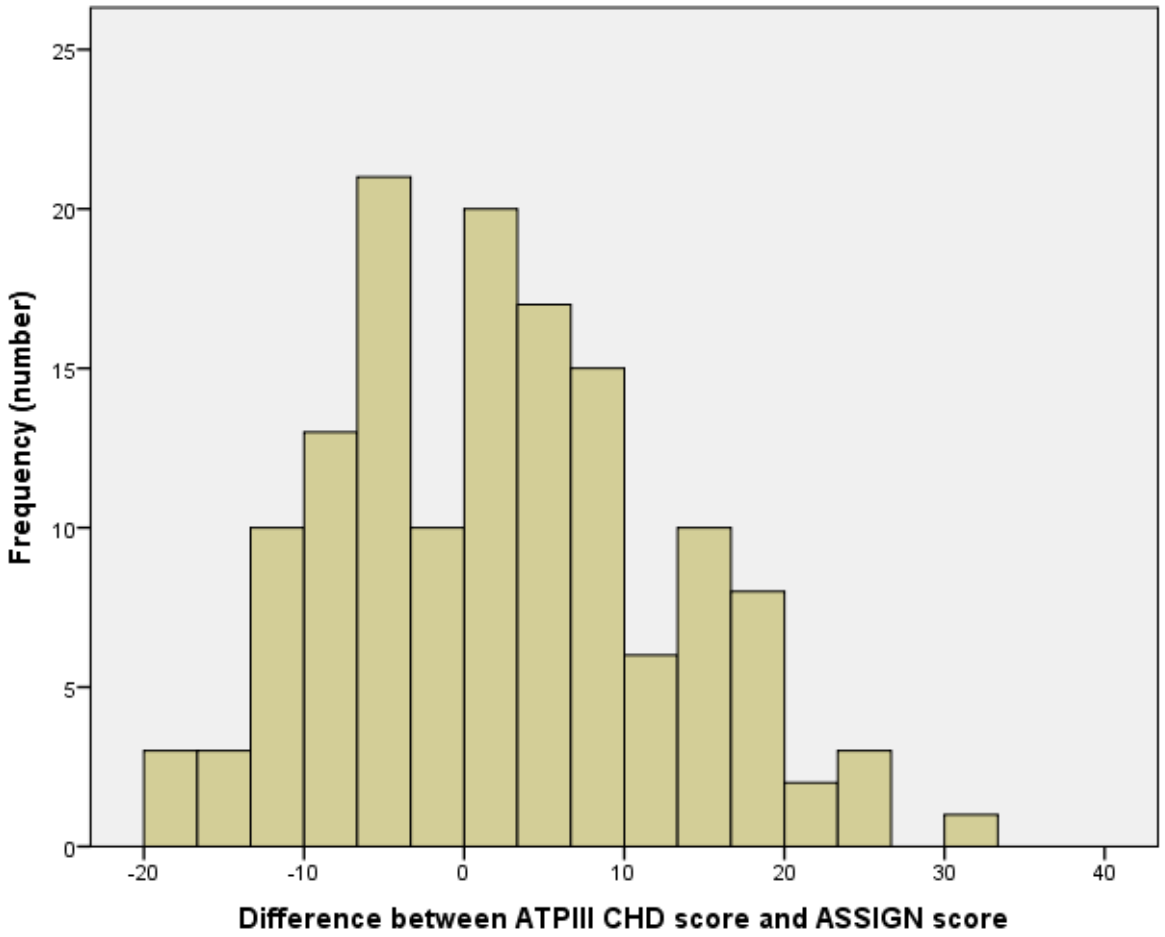


Figure 3.11: Distribution of difference between ATPIII derived CHD risk score and ASSIGN derived CV risk score in participants ineligible to enter TASCFORCE study due to high predicted CHD risk using ATPIII guidelines



Difference calculated by subtracting ATPIII score from ASSIGN score for each participant.

3.3.4. Correlation of BNP with baseline cardiovascular risk factors

Baseline characteristics are described for the 4 quartiles of participants based on BNP level for men in table 3.8 and for women in table 3.9. For men the 25th percentile was 4.9 pg/ml, the median was 7.5 pg/ml and the 75th percentile was 13.8 pg/ml. Compared to men with a BNP in the lowest quartile those with a BNP in the top quartile were older, had a lower diastolic blood pressure, lower resting heart rate, higher HDL, lower triglycerides, slightly lower BMI and were less likely to come from areas of multiple deprivation. They also had a slightly higher predicted CHD risk. The differences in lipid levels, blood pressure and BMI were all small and within "normal" clinical ranges. For women the 25th percentile was 8.5 pg/ml, the median was 15.3 pg/ml and the 75th percentile was 25.2 pg/ml. Compared to women with a BNP in the lowest quartile those with a BNP in the top quartile were also older, had a lower resting heart rate, triglycerides, and higher HDL but also had a slightly higher systolic blood pressure. They also had a slightly higher predicted 10 year CHD risk but this difference was less than in the men.

Table 3.8: Baseline characteristics of male participants according to BNP level

Baseline characteristics		1st quartile (n= 523)	2nd quartile (n= 352)	3rd quartile (n= 433)	4th quartile (n= 432)	p value*
Median (IQR) age (years)		47.4 (9.0)	50.6 (10.4)	51.8 (11.7)	54.6 (12.9)	**<0.001**
No (%) current smokers		67 (12.8)	31 (8.8)	42 (9.7)	46 (10.6)	0.30
No (%) former smokers		132 (25.3)	121 (34.4)	124 (28.6)	126 (29.1)	0.18
No (%) never smokers		323 (61.9)	199 (56.5)	266 (61.4)	260 (60.0)	0.59
Mean (SD) systolic BP(mmHg)		124.7 (10.4)	124.8 (10.8)	125.3 (10.7)	125.1 (11.3)	0.541
Mean (SD) diastolic BP(mmHg)		76.4 (8.8)	76.0 (9.3)	75.6 (8.7)	74.6 (8.8)	**0.001**
Mean (SD) pulse pressure (mmHg)		48.2 (9.6)	48.8 (9.7)	49.7 (9.6)	50.5 (9.7)	**<0.001**
Median (IQR) heart rate (beats per min)		66.0 (14)	64.0 (14)	62.0 (11)	60.0 (13)	**<0.001**
Mean (SD) total cholesterol (mmol/L)		5.46 (0.96)	5.52 (1.00)	5.45 (0.96)	5.40 (0.96)	0.30
Mean (SD) high density lipoprotein (mmol/l)		1.10 (0.37)	1.15 (0.36)	1.23 (0.38)	1.28 (0.39)	**<0.001**
Mean (SD) low density lipoprotein (mmol/l)		3.46 (0.87)	3.51 (0.96)	3.43 (0.87)	3.39 (0.87)	0.24
Median (IQR) triglycerides (mmol/l)		1.70 (1.50)	1.73 (1.38)	1.49 (1.27)	1.51 (5.67)	**<0.001**
Median (IQR) body mass index (kg/m^2)		27.7 (4.9)	27.2 (4.8)	26.7 (4.4)	26.5 (4.9)	**<0.001**
Median (IQR) weight (kg)		85.0 (18.8)	84.0 (17.6)	83.0 (17.9)	82.9 (16.2)	**0.009**
Mean (SD) height (cm)		175.4 (6.4)	175.4 (6.5)	175.6 (6.7)	176.1 (6.3)	0.10
Mean (SD) waist circumference (cm)		94.3 (11.4)	94.5 (11.4)	92.0 (10.9)	92.7 (12.4)	**0.04**
Median (IQR) 10 year CHD event risk estimation using ATPIII algorithm (%)		6.0 (5.0)	6.0 (6.0)	6.0 (6.0)	8.0 (8.0)	**<0.001**
No (%) with family history of CVD		99 (19.0)	63 (18.0)	93 (21.5)	98 (22.6)	0.16
SIMD, Number (%)	1	28 (5.4)	17 (4.9)	22 (5.1)	14 (3.2)	**0.047**
	2	31 (5.9)	14 (4.0)	24 (5.5)	17 (3.9)	
	3	47 (9.0)	35 (9.9)	28 (6.5)	32 (7.4)	
	4	27 (5.2)	21 (6.0)	23 (5.3)	27 (6.2)	
	5	30 (5.7)	16 (4.5)	29 (6.7)	24 (5.5)	
	6	52 (10.0)	26 (7.4)	40 (9.2)	48 (11.1)	
	7	81 (15.5)	59 (16.8)	58 (13.4)	72 (16.7)	
	8	98 (18.8)	78 (22.2)	97 (22.4)	75 (17.3)	
	9	92 (17.6)	62 (17.6)	77 (17.8)	82 (18.9)	
	10	34 (6.5)	23 (6.5)	34 (7.9)	42 (9.7)	

SD=standard deviation, IQR=inter-quartile range, SIMD=Scottish Index of Multiple Deprivation, CV=cardiovascular.*comparison of 4th quartile with 1st quartile. Unpaired t-test was used for normally distributed variables, Mann-Whitney test for skewed and ranked variables and Chi-square test for binomial variables. SIMD was treated as a continuous variable for the purpose of analysis. 25th percentile=4.9 pg/ml, median=7.5 pg/ml and 75th percentile=13.8 pg/ml.

Table 3.9: Baseline characteristics of female participants according to BNP level.

Baseline characteristics		1st quartile (n= 671)	2nd quartile (n= 679)	3rd quartile (n= 661)	4th quartile (n= 672)	P value*
Median (IQR) age (years)		49.5 (9.8)	50.9 (11.7)	52.4 (12.3)	54.4 (13.6)	**<0.001**
No (%) current smokers		131 (19.5)	95 (14.0)	80 (12.1)	80 (11.9)	**<0.001**
No (%) former smokers		188 (28.0)	183 (27.0)	180 (27.2)	172 (25.7)	0.38
No (%) never smokers		353 (52.5)	401 (59.1)	401 (60.1)	414 (62.0)	**<0.001**
Mean (SD) systolic BP(mmHg)		120.2 (12.4)	120.6 (12.0)	120.5 (12.2)	121.9 (12.3)	**0.010**
Mean (SD) diastolic BP(mmHg)		71.9 (9.5)	71.9 (9.0)	72.0 (9.1)	71.6 (9.4)	0.53
Mean (SD) pulse pressure (mmHg)		48.3 (9.7)	48.8 (9.5)	48.5 (9.7)	50.3 (9.9)	**<0.001**
Median (IQR) heart rate (beats per min)		69.0 (13)	66.0 (12)	65.0 (11)	63.0 (12)	**<0.001**
Mean (SD) total cholesterol (mmol/L)		5.43 (1.03)	5.51 (1.05)	5.53 (1.01)	5.50 (1.01)	0.20
Mean (SD) high density lipoprotein (mmol/l)		1.44 (0.42)	1.52 (0.42)	1.53 (0.41)	1.56 (0.40)	**<0.001**
Mean (SD) low density lipoprotein (mmol/l)		3.32 (0.90)	3.40 (0.95)	3.42 (0.88)	3.35 (0.93)	0.54
Median (IQR) triglycerides (mmol/l)		1.28 (1.09)	1.21 (0.93)	1.17 (0.87)	1.17 (0.92)	**0.005**
Median (IQR) body mass index		26.2 (6.0)	25.7 (6.1)	25.9 (6.0)	25.7 (5.8)	0.15
Median (IQR) weight (kg)		68.2 (16.3)	68.0 (17.1)	68.0 (16.4)	68.9 (16.0)	0.75
Mean (SD) height (cm)		161.4 (6.2)	162.0 (6.1)	162.5 (6.4)	162.2 (6.5)	**0.034**
Mean (SD) waist circumference (cm)		84.6 (12.8)	83.2 (13.0)	83.8 (12.5)	82.9 (12.8)	**0.016**
Median (IQR) 10 year CHD event risk estimation using ATPIII algorithm (%)		1.0 (2.0)	1.0 (2.0)	1.0 (2.0)	1.0 (2.0)↑	**0.001**
No (%) with family history of CVD		172 (25.6)	194 (28.6)	184 (27.8)	172 (25.7)	0.97
SIMD, Number (%)	1	38 (5.7)	36 (5.3)	25 (3.8)	37 (5.5)	0.401
	2	48 (7.1)	43 (6.3)	32 (4.8)	42 (6.3)	
	3	61 (9.1)	51 (7.5)	60 (9.1)	43 (6.4)	
	4	38 (5.7)	43 (6.3)	36 (5.4)	35 (5.2)	
	5	43 (6.4)	45 (6.6)	42 (6.3)	40 (6.0)	
	6	57 (8.5)	71 (10.5)	70 (10.6)	60 (9.0)	
	7	106 (15.8)	90 (13.3)	105 (15.9)	112 (16.7)	
	8	110 (16.4)	127 (18.7)	125 (18.9)	133 (19.9)	
	9	105 (15.6)	135 (19.9)	117 (17.7)	129 (19.3)	
	10	64 (9.5)	36 (5.3)	50 (7.6)	36 (5.4)	

SD=standard deviation, IQR=inter-quartile range, SIMD=Scottish Index of Multiple Deprivation, CV=cardiovascular.
*comparison of 4th quartile with 1st quartile. Unpaired t-test was used for normally distributed variables, Mann-Whitney test for skewed and ranked variables and Chi-square test for binomial variables. SIMD was treated as a continuous variable for the purpose of analysis. 25th percentile=8.5 pg/ml, median=15.3 pg/ml and 75th percentile=25.2 pg/ml.

Linear stepwise multiple regression modelling demonstrated that age, female sex, absence of ex-smoking status (but not current smoking status), lower heart rate, higher HDL and lower total cholesterol were associated with higher log10 serum BNP levels (table 3.10). The original model included age, gender, smoking status, systolic BP, diastolic BP, heart rate, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, BMI, waist circumference, family history of cardiovascular disease, SIMD and predicted cardiovascular risk score.

Table 3.10: Association of baseline cardiovascular risk factors with log10 BNP levels: linear stepwise multivariable regression analysis

Variable	Coefficient (95% CI)	p value
Age (years)	0.010 (0.009, 0.011)	<0.001
Male sex	-0.211 (-0.230, -0.192)	<0.001
Ex-smoker	-0.026 (-0.045, -0.006)	0.01
Current smoker	-0.009 (-0.036, 0.017)	0.49
Heart rate (bpm)	-0.006 (-0.007, -0.005)	<0.001
Total cholesterol (mmol/l)	-0.020 (-0.028, -0.011)	<0.001
HDL (mmol/l)	0.055 (0.033, 0.076)	<0.001

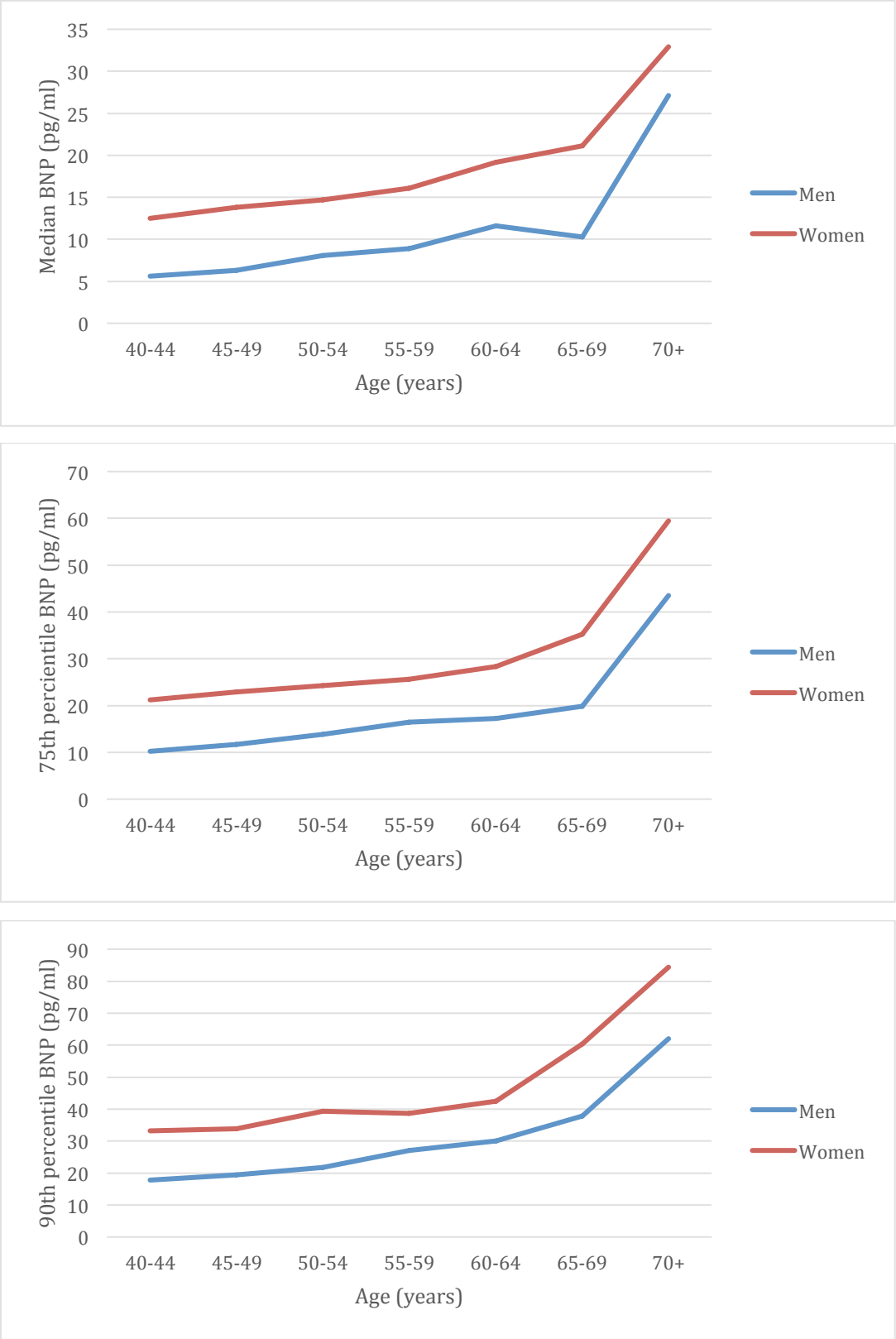
HDL=high density lipoprotein, bpm = beats per minute, CI=confidence interval.

As age and gender have a large effect on BNP age and sex specific BNP median, 75th and 80th percentiles are summarised in table 3.11 and graphically illustrated in figure 3.12.

Table 3.11: Age and sex specific BNP median, 75th and 90th percentiles

Age (years)	Men				Women			
	n	Median	75th percentile	90th percentile	n	Median	75th percentile	90th percentile
40-44	402	5.6	10.2	17.8	536	12.5	21.2	33.2
45-49	430	6.3	11.7	19.5	617	13.8	22.9	33.9
50-54	348	8.1	13.8	21.8	554	14.7	24.3	39.4
55-59	279	8.9	16.4	27.1	451	16.1	25.6	38.6
60-64	175	11.6	17.3	30.1	307	19.2	28.4	42.4
65-69	68	10.3	19.8	37.9	132	21.1	35.3	60.4
70+	34	27.1	43.5	62.1	78	32.9	59.5	84.4

Figure 3.12: Age and gender specific BNP median (top), 75th percentile (middle) and 90th percentiles (bottom)



4. Results part 2 – MRI results

4.1. Participant acceptability of MRI scan

17 of those found to be eligible based on their original BNP result were found to be no longer eligible for scanning when their BNP was rechecked (the BNP cut off was changed after 200 people had been screened as described above). A substudy of participants of South Asian ethnicity was recruited to ensure diversity comparable with the UK population statistics. All recruits in this substudy were offered an MRI scan regardless of their BNP result. 30 South Asian participants were offered a scan 20 of whom had a BNP below their gender cut off. This resulted in 2050 participants being invited for an MRI scan.

Of the 2050 participants eligible for or offered an MRI scan 373 (18.2%) did not consent for a scan and 12 (0.6%) failed to attend for their MRI scan appointment.

1528 (74.8% of those invited) completed or partially completed the scan protocol. Of these 26 (1.3%) only partially completed the scan before it was abandoned due to claustrophobia. Any images obtained before the scan was abandoned were used for analysis where suitable.

101 participants (4.9%) had their scan abandoned completely. In the majority of cases (83) this was due to claustrophobia. Other scans were abandoned due to large body habitus (3), inability to gain IV access (7), becoming unwell during cannulation (4), tissuing of intravenous access (2) or other technical issues (2). 34 (1.7%) were not safe to scan due to presence of metalwork. The characteristics of those who did not complete scanning and those who did have a scan are summarised in table 4.1. More were men, had a slightly higher blood pressure and resting heart rate, and slightly lower HDL.

Table 4.1: Characteristics of those who had an MRI scan and those who declined or were unable to complete a scan

Variable		Underwent MRI scan (n=1528)	Unable/declined to have MRI scan (n=538)	*p value
No (%) men		579 (37.9)	233 (43.3)	**0.03**
Median (IQR) age (years)		53.5 (12.2)	52.6 (13.3)	0.57
No (%) current smokers		165 (10.8)	57 (10.6)	0.88
No (%) former smokers		417 (27.3)	150 (27.9)	0.81
No (%) never smokers		940 (61.5)	330 (61.3)	0.90
Mean (SD) systolic BP(mmHg)		122.4 (12.1)	123.7 (11.7)	**0.046**
Mean (SD) diastolic BP(mmHg)		72.8 (9.2)	73.8 (9.3)	**0.02**
Median (IQR) heart rate (beats per min)		62 (12)	64 (11)	**<0.001**
Mean (SD) total cholesterol (mmol/l)		5.51 (0.96)	5.51 (1.02)	0.89
Mean (SD) high density lipoprotein (mmol/l)		1.43 (0.42)	1.38 (0.39)	**0.04**
Mean (SD) low density lipoprotein (mmol/l)		3.39 (0.87)	3.41 (0.93)	0.78
Median (IQR) triglycerides (mmol/l)		1.33 (0.98)	1.41 (0.98)	0.09
Median (IQR) body mass index		26.1 (5.3)	26.3 (6.0)	0.15
Mean (SD) waist circumference (cm)		86.0 (16.0)	87.0 (17.0)	0.10
Median (IQR) CHD risk score		2 (5)	3 (5)	0.19
Median (IQR) ASSIGN score		7.4 (7.9)	7.8 (8.8)	0.18
Number (%) with family history of CV disease		392 (25.7)	128 (23.8)	0.39
SIMD Number (%)	1	65 (4.3)	23 (4.3)	0.14
	2	79 (5.2)	29 (5.4)	
	3	101 (6.6)	50 (9.3)	
	4	77 (5.0)	39 (7.2)	
	5	95 (6.2)	31 (5.8)	
	6	167 (10.9)	40(7.4)	
	7	248 (16.2)	91 (16.9)	
	8	297 (19.4)	107 (19.9)	
	9	279 (18.3)	92 (17.1)	
	10	117 (7.7)	35 (6.5)	

SD=standard deviation, IQR=inter-quartile range, SIMD=Scottish Index of Multiple Deprivation, CV=cardiovascular, CHD=coronary artery disease, MRI=magnetic resonance imaging.
*Unpaired t-test was used for normally distributed variables, Mann-Whitney test for skewed and ranked variables and Chi-square test for binomial variables. SIMD was treated as a continuous variable for the purpose of analysis.

4.2. Incidental findings on MRI scan

All scans were reviewed by a radiologist for the presence of incidental findings needing further review or investigation. 32 participants (2.1% participants scanned) had an incidental finding on their MRI scan. The nature of the incidental findings are summarised in table 4.2. They have been categorised based on the abnormality. Structural cardiac abnormalities included cardiomyopathies, septal defects and enlargement of cardiac chambers. Benign masses include abnormalities seen on MRI suggesting a possible mass-some of these turned out to be not present on further imaging. Peripheral arterial abnormalities included significant occlusions, aneurysms or decreased flow suggesting a possible stenosis.

Depending on the nature of the radiological incidental finding review by the trial medical team, GP, further investigations, referral to an appropriate specialist or initiation of medication were arranged as appropriate. Table 4.3 summarises the activity arising as a result of the incidental findings. All MRI incidental finding reports were reviewed by the trial team. Due to patient confidentiality the final outcome and diagnosis of those referred for specialist review is not known.

Table 4.2: Summary of MRI incidental findings requiring clinical review and/or further investigation

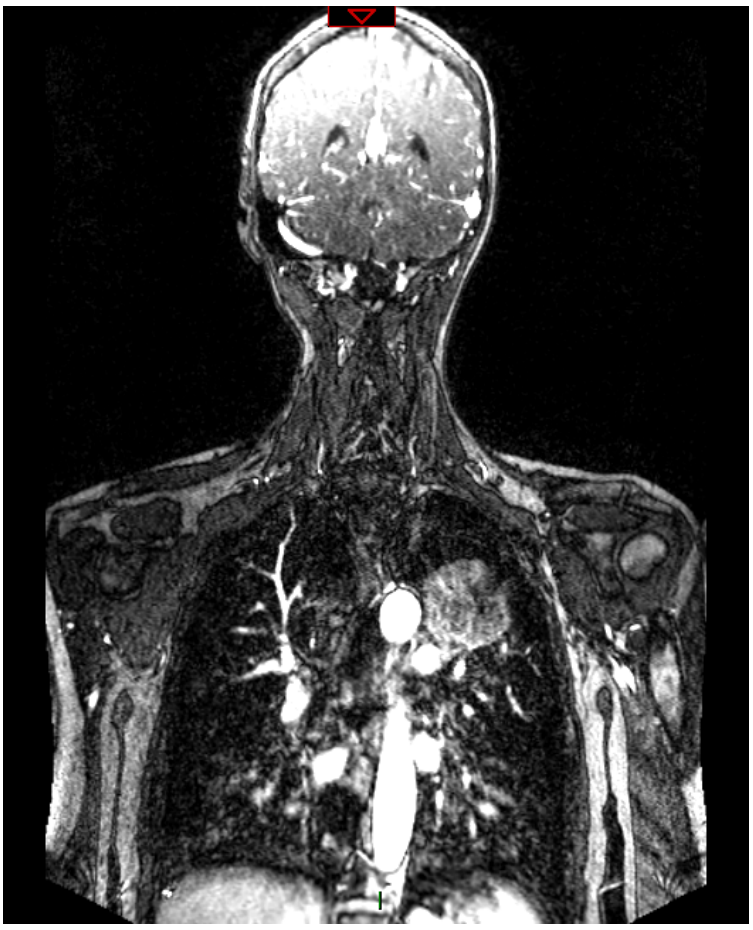
Nature of finding	Frequency
Myocardial infarct detected by delayed enhancement	1
Structural cardiac abnormality	7
Benign mass	10
Malignant mass	1
Peripheral arterial abnormality	6
Anatomical variant/malformation	5
Other finding	2

Table 4.3: Activity arising as a result of MRI incidental findings

Activity	**Number of participants**
Investigations	
Abdominal/pelvic ultrasound scan	7
Vascular ultrasound scan	2
Plain x-ray	1
Echocardiogram	6
Other investigation*	3
Review	
Review by study doctor	6
Review by GP	9
Referral and review to hospital specialist	17
Intervention by study team	
Medication started on advice of study doctor	2

*Other investigations include exercise tolerance tests, blood tests.

Figure 4.1: A left lung mass (probably malignant) seen on a post contrast MRI scan in a female TASCFORCE participant



4.3. MRI derived left ventricular results

4.3.1. Left ventricular measures

1515 (n=574, 37.9% male) participants completed the cardiac MRI scan and produced images suitable for analysis. 15 participants did not have images suitable for analysis due to either motion artefacts or slices missing making reliable assessment of parameters impossible). The baseline clinical characteristics of those who underwent scanning are presented by gender in table 4.4. Summary statistics by gender for the baseline left ventricular measurements including left ventricular mass/end diastolic volume ratio (an indicator of cardiac remodelling) are given in table 4.5. All the measurements were significantly higher in men compared to women except ejection fraction which was slightly higher in women. Relationships of left ventricular mass with height, weight, BMI and body surface area (BSA) are shown in figures 4.2, 4.3 and 4.4.

Table 4.4: Descriptive characteristics of participants who underwent cardiac MRI imaging

Variable	Men (n=574)	Women (n=941)
Median (IQR) age (years)	53.3 (11.9)	53.9 (12.5)
No (%) current smokers	51 (8.9)	113 (12.0)
No (%) former smokers	162 (28.2)	251 (26.7)
No (%) never smokers	359 (62.5)	573 (60.9)
Mean (SD) systolic BP(mmHg)	125.1 (10.9)	120.9 (12.5)
Mean (SD) diastolic BP(mmHg)	74.8 (8.8)	71.5 (9.3)
Median (IQR) heart rate (beats per min)	60 (12)	63 (11)
Median (IQR) body mass index	26.6 (4.4)	26.6 (5.6)
Median (IQR) weight (kg)	83.1 (16.1)	68.1 (15.3)
Mean (SD) height (cm)	176.1 (6.5)	162.5 (6.2)
Mean (SD) waist circumference (cm)	92.4 (11.4)	82.9 (12.4)
Mean (SD) BSA (m^2)	2.02 (0.17)	1.78 (0.18)
Median (IQR) CHD risk score	7.0 (6.0)	1.0 (2.0)
Number (%) with family history of CV disease	131 (22.8)	256 (27.2)

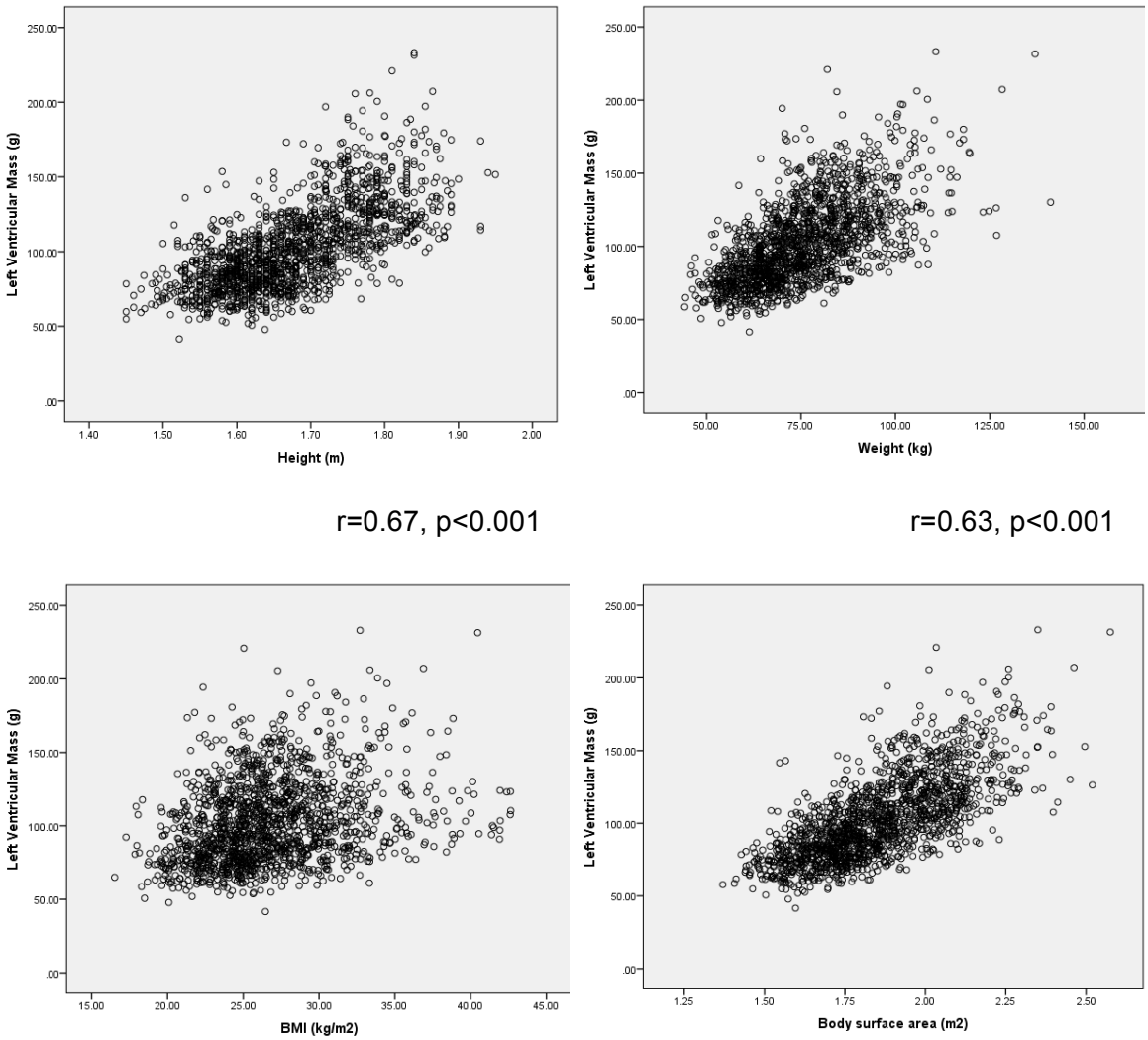
CHD=coronary heart disease, BP=blood pressure, BSA=body surface area (calculated using the Dubois formula), SD=standard deviation, IQR=inter-quartile range.

Table 4.5: Left ventricular characteristics by gender

	Men (n=574)		Women (n=941)		p value*
	Mean	SD	Mean	SD	
LV mass (g)	129.2	24.4	87.0	16.7	<0.001
LV end diastolic volume (ml)	155.0	27.7	119.6	21.1	<0.001
LV end systolic volume (ml)	50.2	14.8	37.1	12.0	<0.001
LVM/LVEDV (g/ml)	0.85	0.16	0.74	0.13	<0.001
Ejection fraction (%)	67.9	6.2	69.3	6.6	<0.001
Stroke volume (ml)	104.8	19.0	82.5	14.2	<0.001
Cardiac output (l/min)	6.46	1.20	5.47	1.13	<0.001

*Comparison between men and women using independent samples t-test. LV=left ventricular, LVM=left ventricular mass, LVEDV=left ventricular end diastolic volume, SD=standard deviation.

Figure 4.2: Scatterplots of left ventricular mass and height (top left), weight (top right), body mass index (bottom left), body surface area (bottom right) for both men and women



r=0.67, p<0.001

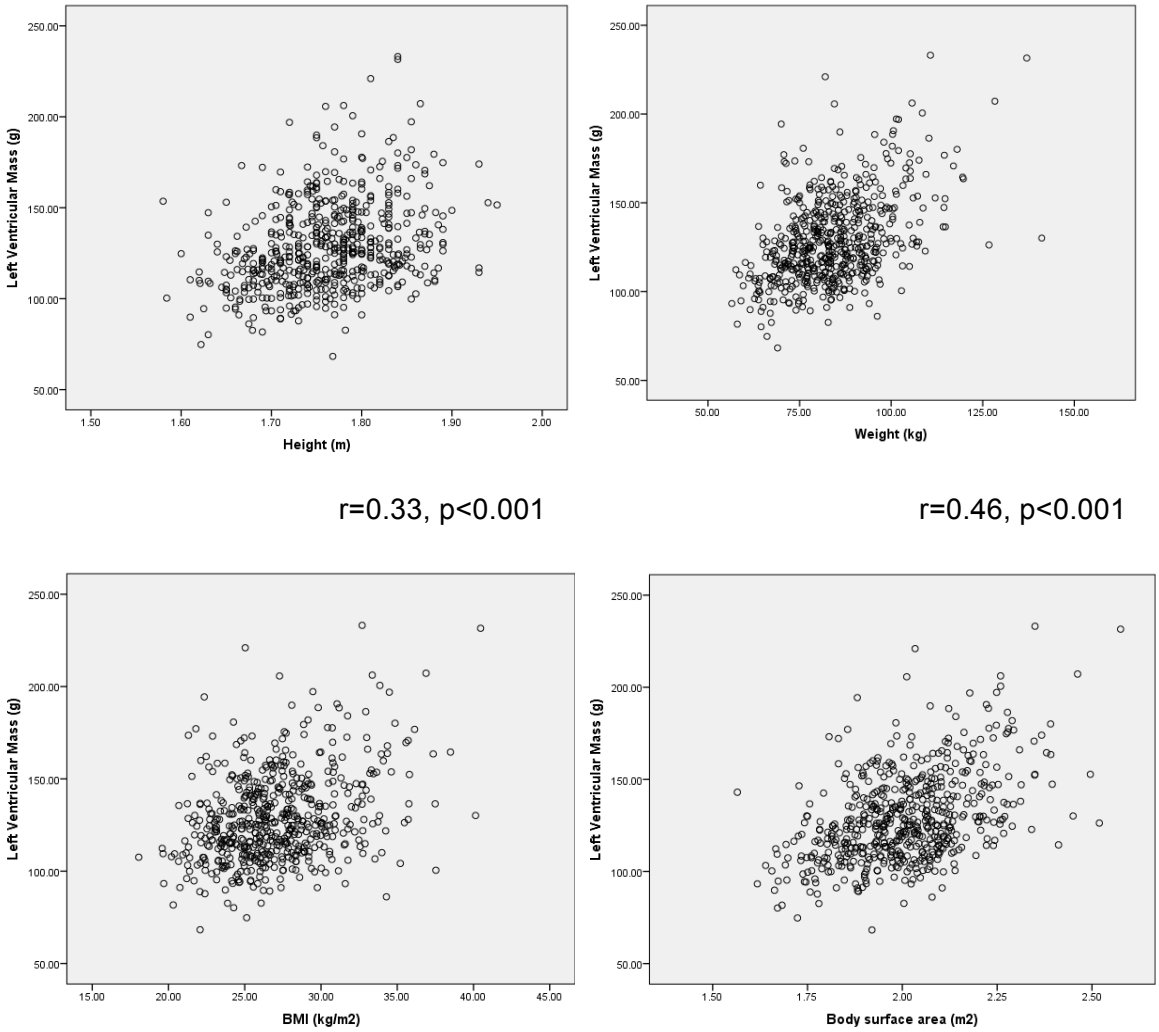
r=0.63, p<0.001

r=0.29, p<0.001

r=0.71, p<0.001

Statistics shown are Pearson correlation coefficients for association between the respective variables. Body surface area is calculated using the Dubois formula.

Figure 4.3: Scatterplots of left ventricular mass and height (top left), weight (top right), body mass index (bottom left), body surface area (bottom right) for men

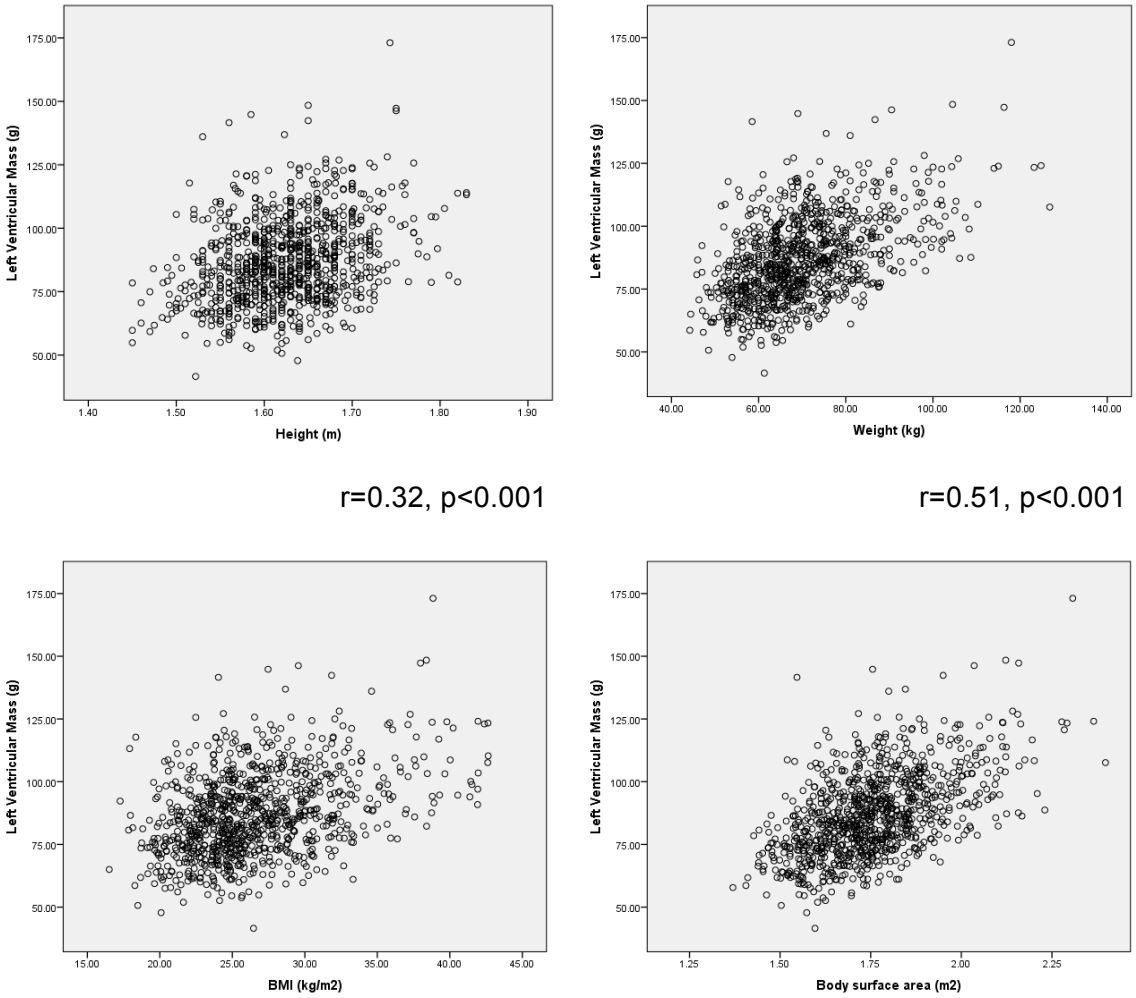


r=0.33, p<0.001 r=0.46, p<0.001

r=0.33, p<0.001 r=0.47, p<0.001

Statistics shown are Pearson correlation coefficients for association between the respective variables. Body surface area is calculated using the Dubois formula.

Figure 4.4: Scatterplots of left ventricular mass and height (top left), weight (top right), body mass index (bottom left), body surface area (bottom right) for women



r=0.32, p<0.001

r=0.51, p<0.001

r=0.40, p<0.001

r=0.54, p<0.001

Statistics shown are Pearson correlation coefficients for association between the respective variables. Body surface area is calculated using the Dubois formula.

Left ventricular mass indexed (LVMI) for height, height$^{1.7}$, height$^{2.7}$, and BSA using DuBois and Mosteller formulae are given in table 4.6. LVMI using each of the methods was significantly higher in men than women.

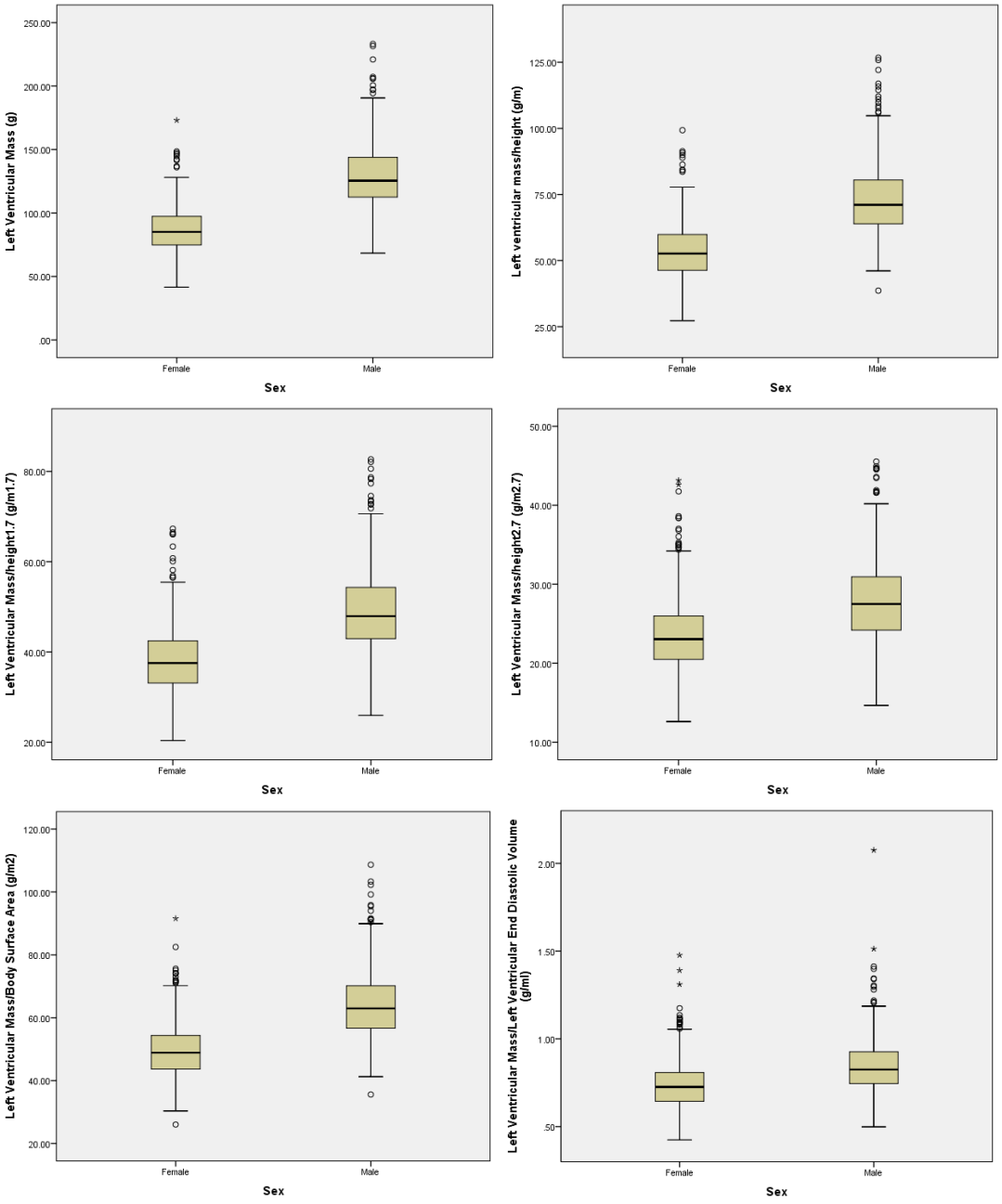
Table 4.6: Left ventricular mass index (LVMI) by height, height$^{1.7}$, height$^{2.7}$, and body surface area (BSA) using DuBois and Mosteller formulae

	Men		Women		
	Mean	SD	Mean	SD	p value*
LV mass/height (g/m)	73.2	13.11	53.5	9.82	<0.001
LV mass/height$^{1.7}$ (g/m$^{1.7}$)	49.3	8.70	38.1	6.95	<0.001
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	28.0	5.03	23.5	4.41	<0.001
LV mass/BSA (Dubois formula) (g/m^2)	64.3	10.6	49.5	8.1	<0.001
LV mass/BSA (Mosteller formula) (g/m^2)	63.8	10.5	48.9	8.0	<0.001

LV=left ventricular, BSA=body surface area, SD=standard deviation. *comparison is between men and women using independent samples t-test.

The distributions of LVM and LVMI using height, height$^{1.7}$, height$^{2.7}$, and BSA (using both Dubois and Mosteller formulae) for men and women are shown in figure 4.5.

Figure 4.5: Boxplots of distribution of left ventricular mass and left ventricular mass index (LVMI) for men and women. From top left to bottom right: LVM, LVMI (height), LVMI (height$^{1.7}$), LVMI (height$^{2.7}$), LVMI (BSA using Dubois calculation) and LVM/end diastolic volume ratio



Correlations of LVMI using the different methods of indexing with height, weight, BSA and BMI are summarised in table 4.7 to give an indication if indexing has corrected for body size. The LVM (not indexed) is given for comparison. Indexing by height$^{2.7}$ reduces the correlation with height greater than height$^{1.7}$ or height. Indexing my BSA reduces correlation with BMI the most whereas indexing for height increases the degree of correlation.

Table 4.7: Correlations between left ventricular mass index and measures of body size

Indexing method for LVMI	Correlation			
	Height	Weight	BSA (using Dubois)	BMI
LVM (not indexed)	r=0.67, p<0.001	r=0.63, p<0.001	r=0.71, p<0.001	r=0.29, p<0.001
Height	r=0.54, p<0.001	r=0.59, p<0.001	r=0.34, p<0.001	r=0.64, p<0.001
Height1.7	r=0.41, p<0.001	r=0.55, p<0.001	r=0.37, p<0.001	r=0.56, p<0.001
Height2.7	r=0.18, p<0.001	r=0.44, p<0.001	r=0.41, p<0.001	r=0.40, p<0.001
BSA (using Dubois)	r=0.48, p<0.001	r=0.35, p<0.001	r=0.42, p<0.001	r=0.08, p=0.002
BSA (using Mosteller)	r=0.48, p<0.001	r=0.32, p<0.001	r=0.40, p<0.001	r=0.03, p=0.261

Correlations are Pearson coefficients. LVM=left ventricular mass, LVMI=left ventricular mass indexed, BSA=body surface area, BMI=body mass index.

The measures of left ventricular volume and function indexed for height, height$^{1.7}$, height$^{2.7}$, BSA (using Dubois formula) and BSA (using Mosteller formula) are summarised in table 4.8. Ejection fraction remained higher in women than men whichever indexing method was used. All the other measures were higher in men.

Table 4.8: Means and standard deviations of left ventricular measurements indexed for height, height$^{1.7}$, height$^{2.7}$, BSA (using Dubois formula) and BSA (using Mosteller formula)

Indexed for height					
	Men		Women		
Variable	Mean	SD	Mean	SD	p value*
LVEDV (ml)	87.8	14.9	73.5	12.1	<0.001
LVESV (ml)	28.4	8.2	22.8	7.2	<0.001
Ejection fraction (%)	38.6	3.8	42.7	4.5	<0.001
Stroke volume (ml)	59.4	10.2	50.7	8.2	<0.001
Cardiac output (l/min)	3.66	0.65	3.37	0.67	<0.001
Indexed for height$^{1.7}$					
	Men		Women		
Variable	Mean	SD	Mean	SD	p value*
LVEDV (ml)	59.1	9.9	52.3	8.4	<0.001
LVESV (ml)	19.1	5.5	16.2	5.1	<0.001
Ejection fraction (%)	26.0	2.9	30.5	3.7	<0.001
Stroke volume (ml)	40.0	6.8	36.1	5.8	<0.001
Cardiac output (l/min)	2.46	0.43	2.40	0.48	0.005
Indexed for height$^{2.7}$					
	Men		Women		
Variable	Mean	SD	Mean	SD	p value*
LVEDV (ml)	33.6	5.7	32.3	5.3	<0.001
LVESV (ml)	10.9	3.1	10.0	3.1	<0.001
Ejection fraction (%)	14.8	2.0	18.9	2.8	<0.001
Stroke volume (ml)	22.7	3.9	22.3	3.7	0.027
Cardiac output (l/min)	1.40	0.25	1.48	0.30	<0.001

Continued on next page

Table 4.8 continued

Indexed for BSA (Dubois formula)					
	Men		Women		
Variable	Mean	SD	Mean	SD	p value*
LVEDV (ml)	77.3	13.2	68.1	10.6	<0.001
LVESV (ml)	25.0	7.4	21.1	6.6	<0.001
Ejection fraction (%)	34.0	4.1	39.8	5.2	<0.001
Stroke volume (ml)	52.2	8.9	47.0	7.2	<0.001
Cardiac output (l/min)	3.22	0.55	3.12	0.58	0.001
Indexed for BSA (Mosteller formula)					
	Men		Women		
Variable	Mean	SD	Mean	SD	p value*
LVEDV (ml)	76.7	13.3	67.4	10.6	<0.001
LVESV (ml)	24.8	7.4	20.9	6.5	<0.001
Ejection fraction (%)	33.8	4.1	39.4	5.4	<0.001
Stroke volume (ml)	51.8	8.9	46.5	7.2	<0.001
Cardiac output (l/min)	3.19	0.55	3.08	0.58	<0.001

*p values are for independent t test for difference in means between men and women.

BSA=body surface area, LVEDV=Left ventricular end diastolic volume, LVESV=left ventricular end systolic volume, LVM=left ventricular mass, SD=standard deviation.

4.3.2. Correlation of left ventricular measures with BNP

Correlations between BNP and MRI derived left ventricular measures are summarised in table 4.9. Left ventricular end diastolic volume (both raw and indexed) and stroke volume were weakly associated with BNP in men. The other measures in men and no measures in women were not correlated with BNP. Differences in left ventricular measures between those above and below 75th, 90th and 95th percentiles of BNP are shown in tables 4.10, 4.11 and 4.12 respectively. Mean left ventricular measures in those with a BNP above and below 100pg/ml (cut off used to diagnose heart failure) are shown in table 4.13.

Differences in left ventricular measures between those above and below 75th, 90th and 95th percentiles of BNP are shown in tables 4.10, 4.11 and 4.12 respectively. The only significant differences were a lower cardiac output in those with a BNP greater than the 95th percentile. Women with a high BNP had higher LVMI (using all methods except BSA calculated using the Mosteller formula), higher end systolic volume and lower ejection fraction compared to those with a “normal” BNP. In men the only difference was a lower end diastolic volume.

Table 4.9: Correlations between BNP and MRI derived measures of left ventricular function and size

	Men		Women	
	r	p	r	p
LV mass (g)	0.04	0.39	-0.08	0.82
LVMI (height) (g/m)	0.03	0.46	-0.01	0.74
LVMI (height$^{1.7}$) (g/m$^{1.7}$)	0.03	0.57	-0.02	0.64
LVMI (height$^{2.7}$) (g/m$^{2.7}$)	0.03	0.48	-0.02	0.54
LVMI (BSA using Dubois formula) (g/m^2)	0.06	0.11	-0.02	0.59
LVMI (BSA using Mosteller formula) (g/m^2)	0.07	0.09	-0.02	0.67
LVEDV (ml)	**0.10**	**0.019**	-0.01	0.74
LVEDV/height (ml/m)	**0.10**	**0.014**	-0.02	0.60
LVEDV/height$^{1.7}$ (ml/m$^{1.7}$)	**0.11**	**0.011**	-0.02	0.51
LVEDV/height$^{2.7}$ (ml/m$^{2.7}$)	**0.11**	**0.011**	-0.02	0.48
LVEDV/BSA (using Dubois formula) (ml/m^2)	**0.12**	**0.003**	-0.01	0.72
LVESV (ml)	0.05	0.27	-0.02	0.59
LVESV/height (ml/m)	0.05	0.29	-0.02	0.51
LVESV/height$^{1.7}$ (ml/m$^{1.7}$)	0.04	0.31	-0.03	0.45
LVESV/height$^{2.7}$ (ml/m$^{2.7}$)	0.04	0.33	-0.03	0.39
LVESV/BSA (using Dubois formula) (ml/m^2)	0.06	0.12	-0.02	0.53
LVM/LVEDV (g/ml)	-0.07	0.08	-0.03	0.45
Ejection fraction (%)	0.02	0.60	0.04	0.28
Ejection fraction/height (%/m)	0.02	0.71	0.03	0.43
Ejection fraction/height$^{1.7}$ (%/m$^{1.7}$)	0.01	0.91	0.02	0.50
Ejection fraction/height$^{2.7}$ (%/m$^{2.7}$)	-0.00	0.92	0.02	0.59
Ejection fraction/BSA (using Dubois formula) (%/m^2)	0.06	0.19	0.02	0.60
Stroke volume (ml)	**0.11**	**0.009**	0.04	0.90
Stroke volume/height (ml/m)	**0.11**	**0.007**	0.00	0.92
Stroke volume/height$^{1.7}$ (ml/m$^{1.7}$)	**0.12**	**0.006**	0.00	0.95
Stroke volume/height$^{2.7}$ (ml/m$^{2.7}$)	**0.11**	**0.009**	0.00	0.94
Stroke volume/BSA (using Dubois formula) (ml/m^2)	**0.14**	**0.001**	0.01	0.80
Cardiac output (l/min)	-0.03	0.43	-0.06	0.08
Cardiac output/height (l/min/m)	-0.04	0.35	-0.06	0.07
Cardiac output/height$^{1.7}$ (l/min/m$^{1.7}$)	-0.04	0.31	-0.06	0.08
Cardiac output/height$^{2.7}$ (l/min/m$^{2.7}$)	-0.05	0.28	-0.05	0.11
Cardiac output/BSA (using Dubois formula) (l/min/m^2)	-0.02	0.72	-0.06	0.09

Correlations are Spearman rank correlations. LV=left ventricular, LVMI=left ventricular mass index, BSA=body surface area, LVEDV=left ventricular end diastolic volume, LVESV=left ventricular end systolic volume.

Table 4.10: Comparison of left ventricular measures in different quartiles of BNP

	Men			Women		
	3rd quartile (n= 232)	4th quartile (n= 335)	p value*	3rd quartile (n= 431)	4th quartile (n= 505)	p value*
LV mass (g)	127.9 (21.1)	130.5 (26.3)	0.21	87.3 (16.8)	86.9 (16.6)	0.78
LVMI (height) (g/m)	72.5 (11.4)	73.8 (14.2)	0.25	53.6 (9.8)	53.5 (9.8)	0.87
LVMI (height$^{1.7}$) (g/m$^{1.7}$)	48.8 (7.7)	49.7 (9.4)	0.26	38.1 (6.9)	38.1 (7.0)	0.94
LVMI (height$^{2.7}$) (g/m$^{2.7}$)	27.7 (4.6)	28.2 (5.3)	0.30	23.5 (4.4)	23.5 (4.4)	0.96
LVMI (BSA using Dubois formula) (g/m^2)	63.5 (9.4)	65.0 (11.3)	0.12	49.6 (8.0)	49.4 (8.1)	0.71
LVMI (BSA using Mosteller formula) (g/m^2)	63.0 (9.3)	64.5 (11.2)	0.10	49.0 (7.9)	48.9 (8.0)	0.75
LV end diastolic volume (ml)	153.6 (25.0)	156.6 (29.2)	0.20	120.2 (21.3)	119.3 (20.8)	0.51
LV end systolic volume (ml)	49.6 (13.7)	50.8 (15.5)	0.33	37.7 (12.0)	36.7 (12.1)	0.20
LVM/LVEDV (g/ml)	0.85 (0.16)	0.85 (0.16)	0.95	0.74 (0.13)	0.74 (0.13)	0.85
Ejection fraction (%)	68.0 (6.2)	67.9 (6.3)	0.87	69.0 (6.4)	69.6 (6.8)	0.14
Stroke volume (ml)	104.0 (17.5)	105.8 (19.8)	0.26	82.5 (14.2)	82.6 (14.1)	0.88
Cardiac output (l/min)	6.51 (1.19)	6.44 (1.20)	0.58	5.53 (1.15)	5.44 (1.10)	0.24

Figures given are mean (standard deviation). 1st and 2nd quartiles are not given as this population were not imaged (median BNP was used to determine if offered a scan).
*comparison is between 3rd and 4th BNP quartiles using independent samples t-test. LV=left ventricular, LVMI=left ventricular mass index, BSA=body surface area, LVEDV=left ventricular end diastolic volume.

Table 4.11: Comparison of LV measures above and below 90th percentiles of BNP

	Men			Women		
	≤90th percentile (n=432)	>90th percentile (n=142)	p value*	≤90th percentile (n=743)	>90th percentile (n=198)	p value*
LV mass (g)	128.9 (23.0)	130.3 (28.1)	0.58	87.3 (16.6)	85.9 (17.2)	0.31
LVMI (height) (g/m)	73.0 (12.4)	73.9 (15.1)	0.55	53.7 (9.8)	52.7 (10.0)	0.22
LVMI (height$^{1.7}$) (g/m$^{1.7}$)	49.1 (8.3)	49.7 (9.9)	0.53	38.3 (6.9)	37.5 (7.0)	0.17
LVMI (height$^{2.7}$) (g/m$^{2.7}$)	27.9 (4.9)	28.3 (5.6)	0.52	23.6 (4.4)	23.1 (4.4)	0.13
LVMI (BSA using Dubois formula) (g/m^2)	63.9 (10.0)	65.6 (12.2)	0.10	49.6 (8.0)	49.0 (8.2)	0.27
LVMI (BSA using Mosteller formula) (g/m^2)	63.4 (9.9)	65.2 (12.1)	0.07	49.0 (7.9)	48.4 (8.1)	0.34
LV end diastolic volume (ml)	153.7 (26.9)	158.9 (29.8)	0.06	119.8 (20.8)	119.0 (22.0)	0.67
LV end systolic volume (ml)	49.7 (14.3)	51.6 (16.1)	0.20	37.1 (11.6)	37.4 (13.5)	0.80
LVM/LVEDV (g/ml)	0.85 (0.16)	0.83 (0.15)	0.14	0.74 (0.13)	0.73 (0.14)	0.62
Ejection fraction (%)	67.9 (6.2)	67.9 (6.4)	0.90	69.4 (6.4)	69.1 (7.3)	0.68
Stroke volume (ml)	104.0 (18.7)	107.3 (19.5)	0.08	82.7 (14.1)	81.7 (14.5)	0.38
Cardiac output (l/min)	6.51 (1.21)	6.30 (1.15)	0.06	5.5 (1.13)	5.35 (1.11)	0.08

Figures given are mean (standard deviation). *comparison using independent samples t-test. LV=left ventricular, LVMI=left ventricular mass index, BSA=body surface area, LVEDV=left ventricular end diastolic volume.

Table 4.12: Comparison of LV measures above and below 95th percentiles of BNP

	Men			Women		
	≤95th percentile (n=507)	>95th percentile (n=67)	p value*	≤95th percentile (n=840)	>95th percentile (n=101)	p value*
LV mass (g)	129.2 (23.9)	129.5 (27.7)	0.92	87.1 (16.5)	86.2 (18.6)	0.62
LVMI (height) (g/m)	73.2 (12.9)	73.8 (14.9)	0.73	53.6 (9.7)	52.7 (11.1)	0.44
LVMI (height$^{1.7}$) (g/m$^{1.7}$)	49.2 (8.6)	49.8 (9.8)	0.62	38.2 (6.8)	37.4 (7.9)	0.33
LVMI (height$^{2.7}$) (g/m$^{2.7}$)	27.9 (5.0)	28.5 (5.6)	0.48	23.6 (4.3)	23.0 (5.0)	0.21
LVMI (BSA using Dubois formula) (g/m^2)	64.1 (10.4)	65.9 (12.1)	0.25	49.5 (7.9)	49.1 (9.2)	0.63
LVMI (BSA using Mosteller formula) (g/m^2)	63.6 (10.2)	65.5 (12.0)	0.22	48.9 (7.8)	48.6 (9.2)	0.74
LV end diastolic volume (ml)	154.8 (27.0)	156.3 (32.9)	0.71	119.6 (20.6)	120.0 (24.3)	0.93
LV end systolic volume (ml)	50.1 (14.2)	50.8 (18.8)	0.71	37.0 (11.4)	38.6 (16.5)	0.21
LVM/LVEDV (g/ml)	0.85 (0.16)	0.84 (0.16)	0.87	0.74 (0.13)	0.73 (0.15)	0.72
Ejection fraction (%)	67.9 (6.1)	68.1 (7.4)	0.82	69.4 (6.3)	68.6 (8.9)	0.26
Stroke volume (ml)	104.7 (18.8)	105.5 (20.7)	0.76	82.6 (14.1)	81.2 (15.33	0.39
Cardiac output (l/min)	6.50 (1.20)	6.12 (1.07)	**0.008**	5.50 (1.13)	5.24 (1.05)	**0.020**

Figures given are mean (standard deviation). *comparison using independent samples t-test. LV=left ventricular, LVM=left ventricular mass, LVMI=left ventricular mass index, BSA=body surface area, LVEDV=left ventricular end diastolic volume.

Left ventricular hypertrophy (LVH) was defined as an LVM greater than 2 standard deviations greater than the mean for each gender. This was 177.9g for men and 120.4g for women. Using this definition of LVH 54 participants (20 men and 34 women) had LVH. The median BNP level for those with and without LVH is shown in table 4.13. There were no significant differences between the results.

Concentric left ventricular hypertrophy was defined as an LVM/LVEDV greater than 2 standard deviations greater than the mean for each gender. This was 1.16g/ml for men and 1.00g/ml in women. Using this definition 60 participants (22 men and 38 women) had concentric LVH. The median BNP level for those with and without concentric LVH is shown in table 4.14. There was no significant difference in BNP levels between those with and without concentric LVH.

Table 4.13: Median BNP values for those with and without LVH

	Men			Women		
	No LVH (n=553)	LVH (n=20)	p value*	No LVH (n=906)	LVH (n=34)	p value*
Median (IQR) BNP level (pg/ml)	15.5 (11.9)	19.0 (12.2)	0.37	26.5 (17.4)	23.8 (12.9)	0.18

*comparison is between those with and without LVH using the Mann-Whitney test. LVH=left ventricular hypertrophy and is defined as >mean+2xSD left ventricular mass for gender. IQR=inter-quartile range.

Table 4.14: Median BNP values for those with and without concentric LVH

	Men			Women		
	No cLVH (n=552)	cLVH (n=22)	p value*	No cLVH (n=902)	cLVH (n=39)	p value*
Median (IQR) BNP level pg/ml	15.5 (11.9)	18.3 (11.5)	0.26	26.2 (17.3)	29.5 (22.2)	0.32

*comparison is between those with and without concentric LVH using the Mann-Whitney test. cLVH=concentric left ventricular hypertrophy and is defined as >mean+2xSD left ventricular mass/ left ventricular end diastolic volume for gender. IQR=inter-quartile range.

4.3.3. Correlation of left ventricular measures with cardiovascular risk factors

Univariate analysis of correlations between left ventricular mass and left ventricular mass index and baseline variables are presented for men and women in tables 4.15 and 4.16. Age was weakly inversely correlated with LVM and LVMI (except when indexed for height$^{2.7}$) in men but only with LVM and LVM indexed for height in women. Systolic BP was weakly correlated with LVM and LVMI and diastolic BP was weakly correlated with LVM and LVMI (except when indexed for MSA using the Mosteller formula) in men. Both systolic and diastolic BP were correlated with LVM and LVMI in women with a slightly stronger correlation than in men. Heart rate was negatively correlated with LVM and LVMI in men but only with LVM indexed for BSA in women. HDL was weakly inversely correlated and LDL and triglycerides were weakly positively correlated with LVMI in women but not in men. BMI was correlated with LVM and LVM indexed for height, height$^{1.7}$ and height$^{2.7}$ in both men and women (greater correlation in women). LVM or LVMI were not correlated with predicted CHD risk in men but they were weakly correlated in women.

Table 4.15: Univariate analysis of correlations between left ventricular mass and baseline variables in men

Variable	LV mass (g)	LVMI (height) (g/m)	LVMI ($height^{1.7}$) ($g/m^{1.7}$)	LVMI ($height^{2.7}$) ($g/m^{2.7}$)	LVMI (BSA using DuBois formula) (g/m^2)	LVMI (BSA using Mosteller formula) (g/m^2)
Age (years)	**-0.16 (<0.001)**	**-0.13 (0.002)**	**-0.10 (0.015)**	-0.06 (0.15)	**-0.11 (0.007)**	**-0.11 (0.006)**
Systolic BP (mmHg)	**0.15 (<0.001)**	**0.16 (<0.001)**	**0.17 (<0.001)**	**0.17 (<0.001)**	**0.14 (0.001)**	**0.13 (0.002)**
Diastolic BP (mmHg)	**0.14 (0.001)**	**0.14 (0.001)**	**0.14 (0.001)**	**0.14 (0.001)**	**0.08 (0.045)**	0.07 (0.08)
Heart rate (beats/min)	**-0.16 (<0.001)**	**-0.16 (<0.001)**	**-0.14 (0.001)**	**-0.12 (0.003)**	**-0.20 (<0.001)**	**-0.20 (<0.001)**
Total cholesterol (mmol/l)	-0.03 (0.51)	-0.03 (0.47)	-0.03 (0.50)	-0.03 (0.52)	-0.06 (0.13)	-0.07 (0.10)
HDL (mmol/l)	-0.05 (0.24)	-0.05 (0.25)	-0.04 (0.30)	-0.04 (0.41)	0.05 (0.21)	0.07 (0.11)
LDL (mmol/l)	-0.02 (0.57)	-0.03 (0.47)	-0.03 (0.44)	-0.04 (0.42)	-0.06 (0.14)	-0.07 (0.11)
Triglycerides (mmol/l)	0.03 (0.51)	0.03 (0.49)	0.03 (0.52)	0.02 (0.61)	-0.07 (0.12)	-0.08 (0.05)
BMI (kg/m^2)	**0.28 (<0.001)**	**0.31 (<0.001)**	**0.33 (<0.001)**	**0.33 (<0.001)**	0.03 (0.42)	-0.02 (0.65)
Waist circumference (cm)	**0.18 (<0.001)**	**0.16 (<0.001)**	**0.15 (<0.001)**	**0.12 (0.004)**	-0.07 (0.89)	**-0.11 (0.009)**
Predicted CHD risk score (%/10 years)	-0.07 (0.12)	-0.04 (0.31)	-0.02 (0.67)	-0.01 (0.73)	-0.05 (0.24)	-0.06 (0.17)

Spearman Rank correlations (ρ and (p) values are given) were used. LV=left ventricular, LVMI=left ventricular mass index, BSA=body surface area, LVEDV=left ventricular end diastolic volume, CHD=coronary heart disease, BMI=body mass index, LDL=low density lipoprotein, HDL=high density lipoprotein, BP=blood pressure.

Table 4.16: Univariate analysis of correlations between left ventricular mass and baseline variables in women

Variable	LV mass (g)	LVMI (height) (g/m)	LVMI ($height^{1.7}$) ($g/m^{1.7}$)	LVMI ($height^{2.7}$) ($g/m^{2.7}$)	LVMI (BSA using DuBois formula) (g/m^2)	LVMI (BSA using Mosteller formula) (g/m^2)
Age (years)	**-0.12 (<0.001)**	**-0.09 (0.008)**	-0.06 (0.07)	-0.02 (0.56)	-0.03 (0.30)	-0.03 (0.43)
Systolic BP (mmHg)	**0.21 (<0.001)**	**0.24 (<0.001)**	**0.26 (<0.001)**	**0.27 (<0.001)**	**0.19 (<0.001)**	**0.18 (<0.001)**
Diastolic BP (mmHg)	**0.25 (<0.001)**	**0.26 (<0.001)**	**0.26 (<0.001)**	**0.26 (<0.001)**	**0.19 (<0.001)**	**0.17 (<0.001)**
Heart rate (beats/min)	-0.03 (0.41)	-0.03 (0.42)	-0.03 (0.47)	-0.02 (0.56)	**-0.10 (0.003)**	**-0.11 (0.001)**
Total cholesterol (mmol/l)	0.03 (0.42)	0.04 (0.19)	0.06 (0.09)	**0.08 (0.022)**	0.02 (0.65)	0.01 (0.82)
HDL (mmol/l)	**-0.14 (<0.001)**	**-0.15 (<0.001)**	**-0.15 (<0.001)**	**-0.14 (<0.001)**	-0.04 (0.18)	-0.02 (0.47)
LDL (mmol/l)	0.07 (0.06)	**0.08 (0.017)**	**0.09 (0.007)**	**0.11 (0.002)**	0.04 (0.23)	0.03 (0.37)
Triglycerides (mmol/l)	**0.07 (0.031)**	**0.09 (0.006)**	**0.10 (0.0031**	**0.12 (<0.001)**	0.06 (0.85)	-0.01 (0.70)
BMI (kg/m^2)	**0.37 (<0.001)**	**0.41 (<0.001)**	**0.43 (<0.001)**	**0.44 (<0.001)**	0.05 (0.11)	-0.03 (0.47)
Waist circumference (cm)	**0.34 (<0.001)**	**0.35 (<0.001)**	**0.34 (<0.001)**	**0.32 (<0.001)**	0.04 (0.19)	-0.02 (0.64)
Predicted CHD risk score (%/10 years)	**0.08 (0.018)**	**0.11 (0.001)**	**0.13 (<0.001)**	**0.16 (<0.001)**	**0.10 (0.002)**	**0.09 (0.005)**

Spearman Rank correlations (ρ and (p) values are given) were used. LV=left ventricular, LVMI=left ventricular mass index, BSA=body surface area, LVEDV=left ventricular end diastolic volume, CHD=coronary heart disease, BMI=body mass index, LDL=low density lipoprotein, HDL=high density lipoprotein, BP=blood pressure.

Univariate analysis of correlations between other left ventricular measures and baseline variables are presented for men and women in tables 4.17 and 4.18. Left ventricular volumes and cardiac output were weakly inversely correlated with age in men and women (stronger correlation in women). In men the volumes were inversely associated with heart rate, total cholesterol and LDL. Ejection fraction was correlated with age, systolic BP and total cholesterol, waist circumference and predicted CHD risk. LVM/LVEDV was correlated with systolic and diastolic BP, heart rate, total cholesterol, triglycerides, BMI, waist circumference and predicted CHD risk. None of the correlations were strong. In women ejection fraction was correlated with age, systolic and diastolic BP, total cholesterol, LDL, triglycerides and predicted CHD risk. LVM/LVEDV was correlated with age, systolic and diastolic BP, heart rate, total and LDL cholesterol, triglycerides, BMI, waist circumference and predicted CHD risk and inversely associated with HDL (weak).

Table 4.17: Univariate analysis of correlations between left ventricular measures and baseline variables in men

Variable	LVEDV (ml)	LVESV (ml)	Ejection fraction (%)	Stroke volume (ml)	Cardiac output (ml/min)	LVM/LVEDV (g/ml)
Age (years)	**-0.23** **(<0.001)**	**-0.20** **(<0.001)**	**0.08** **(0.048)**	**-0.19** **(<0.001)**	**-0.15** **(<0.001)**	0.07 (0.10)
Systolic BP (mmHg)	0.00 (0.97)	-0.07 (0.10)	**0.09** **(0.038)**	0.05 (0.25)	**0.11** **(0.006)**	**0.15** **(<0.001)**
Diastolic BP (mmHg)	0.01 (0.91)	-0.03 (0.49)	0.05 (0.27)	0.04 (0.37)	**0.17** **(<0.001)**	**0.13** **(0.002)**
Heart rate (beats/min)	**-0.34** **(<0.001)**	**-0.19** **(<0.001)**	-0.03 (0.43)	**-0.35** **(<0.001)**	**0.17** **(<0.001)**	**0.19** **(<0.001)**
Total cholesterol (mmol/l)	**-0.12** **(0.005)**	**-0.14** **(0.001)**	**0.10** **(0.017)**	**-0.09** **(0.028)**	-0.01 (0.90)	**0.10** **(0.021)**
HDL (mmol/l)	0.02 (0.65)	-0.02 (0.60)	0.05 (0.20)	0.04 (0.31)	-0.05 (0.26)	-0.06 (0.16)
LDL (mmol/l)	-**0.10** **(0.015)**	-**0.10** **(0.027)**	0.05 (0.30)	**-0.10** **(0.020)**	-0.03 (0.46)	0.08 (0.08)
Triglycerides (mmol/l)	-0.07 (0.09)	-**0.09** **(0.027)**	0.07 (0.07)	-0.04 (0.41)	0.08 (0.06)	**0.10** **(0.014)**
BMI (kg/m^2)	**0.12** **(0.004)**	0.05 (0.29)	0.05 (0.22)	**0.15** **(<0.001)**	**0.20** **(<0.001)**	**0.19** **(<0.001)**
Waist circumference (cm)	0.03 (0.47)	-0.04 (0.34)	**0.10** **(0.020)**	0.08 (0.05)	**0.19** **(<0.001)**	**0.16** **(<0.001)**
Predicted CHD risk score (%/10 years)	**-0.23** **(<0.001)**	**-0.20** **(<0.001)**	**0.09** **(0.034)**	**-0.19** **(<0.001)**	-0.05 (0.22)	**0.17** **(<0.001)**

Spearman Rank correlations (ρ and (p) values are given) were used. LV=left ventricular, LVMI=left ventricular mass index, BSA=body surface area, LVEDV=left ventricular end diastolic volume, LVESV=left ventricular end systolic volume, CHD=coronary heart disease, BMI=body mass index, LDL=low density lipoprotein, HDL=high density lipoprotein, BP=blood pressure.

Table 4.18: Univariate analysis of correlations between left ventricular measures and baseline variables in women

Variable	LVEDV (ml)	LVESV (ml)	Ejection fraction (%)	Stroke volume (ml)	Cardiac output (ml/min)	LVM/LVEDV (g/ml)
Age (years)	**-0.32 (<0.001)**	**-0.29 (<0.001)**	**0.17 (<0.001)**	**-0.25 (<0.001)**	**-0.23 (<0.001)**	**0.19 (<0.001)**
Systolic BP (mmHg)	-0.06 (0.07)	**-0.18 (<0.001)**	**0.21 (<0.001)**	0.04 (0.29)	**0.15 (<0.001)**	**0.29 (<0.001)**
Diastolic BP (mmHg)	0.01 (0.66)	**-0.08 (0.018)**	**0.13 (<0.001)**	**0.07 (0.031)**	**0.18 (<0.001)**	**0.26 (<0.001)**
Heart rate (beats/min)	**-0.13 (<0.001)**	**-0.08 (0.016)**	-0.01 (0.84)	**-0.15 (<0.001)**	**0.23 (<0.001)**	**0.11 (0.001)**
Total cholesterol (mmol/l)	**-0.18 (<0.001)**	**-0.19 (<0.001)**	**0.14 (<0.001)**	**-0.13 (<0.001)**	-0.05 (0.10)	**0.19 (<0.001)**
HDL (mmol/l)	-0.06 (0.07)	-0.03 (0.40)	0.00 (0.99)	**-0.07 (0.039)**	-0.06 (0.07)	**-0.09 (0.007)**
LDL (mmol/l)	**-0.14 (<0.001)**	**-0.15 (<0.001)**	**0.10 (0.003)**	**-0.10 (0.004)**	-0.04 (0.21)	**0.20 (<0.001)**
Triglycerides (mmol/l)	**-0.13 (<0.001)**	**0.15 (<0.001)**	**0.11 (0.001)**	**-0.08 (0.014)**	0.03 (0.35)	**0.19 (<0.001)**
BMI (kg/m^2)	**0.22 (<0.001)**	**0.09 (0.008)**	0.05 (0.13)	**0.24 (<0.001)**	**0.26 (<0.001)**	**0.17 (<0.001)**
Waist circumference (cm)	**0.17 (<0.001)**	0.06 (0.06)	0.05 (0.17)	**0.18 (<0.001)**	**0.22 (<0.001)**	**0.21 (<0.001)**
Predicted CHD risk score (%/10 years)	**-0.23 (<0.001)**	**-0.24 (<0.001)**	**0.16 (<0.001)**	**0.17 (<0.001)**	**-0.09 (0.007)**	**0.30 (<0.001)**

Spearman Rank correlations (ρ and (p) values are given) were used. LV=left ventricular, LVMI=left ventricular mass index, BSA=body surface area, LVEDV=left ventricular end diastolic volume, LVESV=left ventricular end systolic volume, CHD=coronary heart disease, BMI=body mass index, LDL=low density lipoprotein, HDL=high density lipoprotein, BP=blood pressure.

4.3.5. Multivariable analysis of left ventricular measures and risk factors and BNP

For each gender multivariable linear regression analysis was performed to determine which baseline factors were independently associated with LVM, LVMI (using each correction method) and left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), cardiac output, stroke volume, ejection fraction and LVM/LVEDV. The model included age, systolic BP, diastolic BP, heart rate, HDL cholesterol, LDL cholesterol, triglycerides, BMI, waist circumference, smoking status, family history of CVD, SIMD decile and BNP. All variables (including the left ventricular variables) with a positively skewed distribution were log transformed to produce a more normal distribution for the analysis. Results of the models are summarised in tables 4.19, 4.20, 4.21 and 4.22.

In men the strongest independent associations with LVM and/or LVMI were age, BMI and heart rate. Age was independently inversely associated with LVM and LVM indexed using all methods except height$^{2.7}$. Heart rate was independently inversely associated with LVM and LVMI using all indexing methods. BMI was strongly associated with LVM and LVM indexed for height but not for BSA using the Mosteller formula. Systolic blood pressure was weakly associated with LVM and LVMI but diastolic blood pressure was not. Lipid profile (LDL, HDL and triglycerides) and FH were not associated with LVM or LVMI and current smoking status was weakly associated with LVM indexed for height$^{2.7}$ or BSA. Notably BNP did not have any independent association with LVM or LVMI.

In women the strongest independent associations with LVM and/or LVMI were heart rate, age, BMI and current smoking status. Age was independently inversely associated with LVM and LVM indexed for height and BSA but not for height$^{1.7}$ or height$^{2.7}$. Heart rate inversely associated with LVM and LVMI. The association with age and heart rate was weaker in women than in men. As in men BMI was strongly

positively associated with LVM and LVM indexed for height but not for BSA. Current smoking was more strongly associated with LVM and LVMI than in men. Again there was a weak association with systolic blood pressure but also with diastolic blood pressure in women. As in men there was no association with HDL or LDL or, notably, with BNP. Overall the models only accounted for 10-20% and 10-30% of the variability of LVM or LVMI in men and women respectively meaning much of the variability is probably due to unmeasured factors.

Table 4.19: Multivariable analysis of traditional cardiovascular risk factors, socio-demographic factors and BNP in relation to left ventricular mass and left ventricular mass index in men

Variable	log LV mass	log LVMI (height) (g/m)	log LVMI (height$^{1.7}$) (g/m$^{1.7}$)	log LVMI (height$^{2.7}$) (g/m$^{2.7}$)	log LVMI (BSA using dubois formula) (g/m^2)	log LVMI (BSA using Mosteller formula) (g/m^2)
Proportion of variability explained by model$	20.3%	21.5%	22.2%	22.8%	11.8%	11.6%
Risk factor coefficient (95% CI)						
Log Age (years)	**-0.26 (-0.36,-0.15)***	**-0.18 (-0.28,-0.09)***	**-0.13 (-0.23,-0.04)***	-0.06 (-0.16,0.04)	**-0.16 (-0.25,-0.06)***	**-0.16 (-0.26,-0.06)***
Log Heart rate (bpm)	**-0.31 (-0.41,-0.22)***	**-0.30 (-0.39,-0.21)***	**-0.29 (-0.38,-0.20)***	**-0.27 (-0.36,-0.18)***	**-0.29 (-0.38,-0.20)***	**-0.29 (-0.38,-0.20)***
Log Triglycerides (mmol/l)	-0.02 (-0.05,0.02)	-0.02 (-0.05,0.02)	-0.01 (-0.05,0.02)	-0.01 (-0.05,0.02)	-0.01 (-0.04,0.02)	-0.01 (-0.04,0.02)
log BMI (kg/m^2)	**0.40 (0.22,0.58)***	**0.54 (0.37,0.71)***	**0.64 (0.47,0.81)***	**0.78 (0.61,0.95)***	**0.20 (0.03,0.37)#**	0.12 (-0.05,0.29)
log BNP (pg/ml)	0.01 (-0.01,0.04)	0.01 (-0.02,0.04)	0.01 (-0.02,0.04)	0.0078 (-0.02,0.04)	0.02 (-0.01,0.04)	0.02 (-0.01,0.04)
Systolic BP (mmHg)	**0.002 (0.001, 0.004)***	**0.002 (0,0.004)***	**0.002 (0,0.004)#**	**0.0018 (0,0.003)#**	**0.002 (0.001,0.004)***	**0.002 (0.001,0.004)***
Diastolic BP (mmHg)	0.00 (-0.001, 0.003)	0.001 (-0.001,0.003)	0.001 (-0.001,0.003)	0.001 (-0.001,0.003)	0.001 (-0.001,0.003)	0.001 (-0.001,0.003)
HDL (mmol/l)	0.02 (-0.02,0.06)	0.02 (-0.03,0.06)	0.017 (-0.02,0.06)	0.02 (-0.02,0.06)	0.02 (-0.02,0.06)	0.02 (-0.03,0.06)
LDL (mmol/l)	-0.00 (-0.02,0.01)	-0.005 (-0.02,0.01)	-0.006 (-0.02,0.01)	-0.007 (-0.02,0.01)	-0.004 (-0.021,0.012)	-0.004 (-0.021,0.012)
Waist circumference (cm)	0.00 (-0.001,0.003)	0.00 (-0.003,0.001)	**-0.002 (-0.004,0)#**	**-0.004 (-0.006, -0.002)***	-0.002 (-0.004,0)	-0.002 (-0.003,0)
SIMD Decile	0.00 (-0.006,0.006)	-0.002 (-0.007,0.004)	-0.003 (-0.008,0.003)	0.00 (-0.01,0.00)	0.00 (-0.01,0.00)	0.00 (-0.01,0.00)
Ex smoker (v never smoked)	0.01 (-0.02,0.05)	0.02 (-0.02,0.05)	0.02 (-0.02,0.05)	0.02 (-0.02,0.05)	0.02 (-0.01,0.05)	0.02 (-0.02,0.05)
Current smoking (v never smoked)	0.04 (-0.01,0.09)	0.05 (-0.002,0.1)	0.05 (0.01,0.10)	**0.06 (0.01,0.11)#**	**0.06 (0.01,0.11)#**	**0.06 (0.01,0.11)#**
Family history of CVD (v no history of CVD)	-0.01 (-0.05,0.02)	-0.009 (-0.042,0.025)	-0.006 (-0.038,0.027)	0.0 (-0.03,0.03)	-0.01 (-0.04,0.03)	-0.01 (-0.04,0.03)

*Test for significance of coefficient: p<0.01, #test for significance of coefficient: p<0.05.
$Proportion of variability (adjusted r^2) explained by the cardiovascular, demographic and blood markers included in model. CI=confidence interval, LV=left ventricular, LVMI=left ventricular mass index, BSA=body surface area, bpm=beats per minute, BMI=body mass index, BNP=B-type natriuretic peptide, HDL=high density lipoprotein, LDL=low density lipoprotein, SIMD=Scottish index of multiple deprivation, CVD=cardiovascular disease.

Table 4.20: Multivariable analysis of traditional cardiovascular risk factors, socio-demographic factors and BNP in relation to left ventricular mass and left ventricular mass index in women

Variable	log LV mass	log LVMI (height) (g/m)	log LVMI (height$^{1.7}$) (g/m$^{1.7}$)	log LVMI (height$^{2.7}$) (g/m$^{2.7}$)	log LVMI (BSA using DuBois formula) (g/m^2)	log LVMI (BSA using Mosteller formula) (g/m^2)
Proportion of variability explained by model$	25.7%	27.9%	29.0%	29.5%	11.0%	10.8%
Risk factor coefficient (95% CI)						
log Age (years)	**-0.18 (-0.27,-0.10)***	**-0.12 (-0.20,-0.04)***	-0.07 (-0.15,0.01)	-0.01 (-0.09,0.07)	**-0.09 (-0.17,-0.01)#**	**-0.09 (-0.17,-0.01)#**
log Heart rate (bpm)	**-0.20 (-0.28,-0.13)***	**-0.19 (-0.26,-0.12)***	**-0.18 (-0.25,-0.12)***	**-0.17 (-0.24,-0.10)***	**-0.18 (-0.25,-0.11)***	**-0.18 (-0.25,-0.11)***
log Triglycerides (mmol/l)	**-0.03 (-0.06,-0.003)#**	**-0.03 (-0.05,-0.001)#**	-0.02 (-0.05,0.00)	-0.02 (-0.04,0.01)	-0.02 (-0.04,0.00)	-0.02 (-0.04,0.00)
log BMI (kg/m^2)	**0.18 (0.06,0.30)***	**0.30 (0.19,0.41)***	**0.38 (0.27,0.49)***	**0.50 (0.39,0.61)***	-0.07 (-0.18,0.04)	**-0.15 (-0.26,-0.04)***
log BNP (pg/ml)	0.013 (-0.01,0.04)	0.01 (-0.02,0.03)	0.00 (-0.02,0.03)	0.00 (-0.03,0.02)	0.00 (-0.02,0.03)	0.01 (-0.02,0.03)
Systolic BP (mmHg)	**0.003 (0.001,0.004)***	**0.003 (0.001,0.004)***	**0.003 (0.001,0.004)***	**0.003 (0.001,0.004)***	**0.003 (0.001,0.004)***	**0.003 (0.001,0.004)***
Diastolic BP (mmHg)	**0.003 (0.001,0.004)***	**0.002 (0.001,0.004)***	**0.002 (0.001,0.004)***	**0.002 (0.001,0.004)***	**0.002 (0.001,0.004)***	**0.002 (0.001,0.004)***
HDL (mmol/l)	-0.02 (-0.05,0.02)	-0.01 (-0.04,0.02)	-0.01 (-0.04,0.02)	-0.01 (-0.04,0.02)	-0.01 (-0.04,0.02)	-0.01 (-0.04,0.02)
LDL (mmol/l)	0.01 (-0.01,0.02)	0.01 (-0.01,0.01)	0.01 (-0.01,0.02)	0.00 (-0.01,0.02)	0.01 (-0.01,0.02)	0.00 (-0.01,0.02)
Waist circumference (cm)	**0.003 (0.002,0.005)***	**0.00 (0,0.00)#**	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)
SIMD Decile	**0.006 (0.002,0.011)***	0.00 (0,0.01)	0.00 (0.00,0.01)	0.00 (0.00,0.00)	0.00 (0.00,0.01)	0.00 (0.00,0.01)
Ex smoker (v never smoked)	0.00 (-0.03,0.03)	-0.01 (-0.03,0.02)	-0.01 (-0.03,0.01)	-0.02 (-0.04,0.01)	0.00 (-0.03,0.02)	0.00 (-0.03,0.02)
Current smoking (v never smoked)	**0.08 (0.05,0.12)***	**0.08 (0.05,0.12)***	**0.09 (0.05,0.12)***	**0.09 (0.05,0.12)***	**0.09 (0.05,0.12)***	**0.09 (0.05,0.12)***
Family history of CVD (v no family history)	-0.01 (-0.03,0.02)	0.00 (-0.02,0.02)	0.00 (-0.02,0.02)	0.01 (-0.01,0.03)	0.00 (-0.02,0.03)	0.00 (-0.02,0.03)

*Test for significance of coefficient: p<0.01, #test for significance of coefficient: p<0.05.
$Proportion of variability (adjusted r^2) explained by the cardiovascular, demographic and blood markers included in model. CI=confidence interval, LV=left ventricular, LVMI=left ventricular mass index, BSA=body surface area, bpm=beats per minute, BMI=body mass index, BNP=B-type natriuretic peptide, HDL=high density lipoprotein, LDL=low density lipoprotein, SIMD=Scottish index of multiple deprivation, CVD=cardiovascular disease.

Table 4.21: Multivariable analysis of traditional cardiovascular risk factors, socio-demographic factors and BNP in relation to other left ventricular measures in men

Variable	log end diastolic volume (ml)	log end systolic volume (ml)	log stroke volume (ml)	Ejection fraction (%)	log cardiac output (l/min)	log LV mass/LV end diastolic volume (g/ml)
Proportion of variability explained by model$	27.5%	13.3%	24.4%	1.1%	28.2%	8.5%
Risk factor coefficient (95% CI)						
log Age (years)	**-0.26 (-0.36,-0.17)***	**-0.29 (-0.47,-0.11)***	**-0.26 (-0.36,-0.16)***	0.50 (-3.46,4.46)	**-0.26 (-0.36,-0.16)***	0.01 (-0.10,0.11)
log Heart rate (bpm)	**-0.48 (-0.57,-0.39)***	**-0.51 (-0.68,-0.35)***	**-0.46 (-0.55,-0.37)***	0.95 (-2.66,4.57)	**0.54 (0.45,0.63)***	**0.17 (0.07,0.26)***
log Triglycerides (mmol/l)	-0.01 (-0.04,0.02)	-0.02 (-0.08,0.03)	-0.01 (-0.04,0.02)	0.33 (-0.89,1.56)	-0.01 (-0.04,0.03)	-0.01 (-0.04,0.03)
log BMI (kg/m^2)	**0.26 (0.09,0.43)***	**0.40 (0.09,0.71)#**	**0.22 (0.05,0.39)#**	-3.49 (-10.32,3.33)	**0.22 (0.05,0.39)#**	0.14 (-0.04,0.32)
log BNP (pg/ml)	0.02 (0.00,0.05)	0.02 (-0.03,0.07)	0.03 (0.00,0.05)	0.12 (-0.96,1.10)	0.03 (0.00,0.05)	-0.01 (-0.04,0.02)
Systolic BP (mmHg)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.03 (-0.03,0.09)	0.00 (0.00,0.00)	**0.002 (0.000,0.003)#**
Diastolic BP (mmHg)	0.00 (0.00,0.00)	0.00 (0.00,0.01)	0.00 (0.00,0.00)	0.00 (-0.08,0.08)	0.00 (0.00,0.00)	0.00 (0.00,0.00)
HDL (mmol/l)	0.01 (-0.03,0.05)	-0.04 (-0.11,0.04)	0.03 (-0.01,0.07)	1.45 (-0.22,3.12)	0.03 (-0.01,0.07)	0.00 (-0.04,0.05)
LDL (mmol/l)	**-0.02 (-0.04,-0.003)#**	**-0.03 (-0.06,-0.004)#**	-0.01 (-0.03,0.00)	0.42 (-0.25,1.08)	-0.01 (-0.03,0.00)	0.02 (0.00,0.03)
Waist circumference (cm)	0.00 (0.00,0.00)	-0.00 (-0.01,0.00)	0.00 (-0.00,0.00)	0.07 (-0.01,0.15)	0.00 (0.00,0.00)	0.00 (0.00,0.00)
SIMD Decile	0.00 (-0.01,0.00)	-0.01 (-0.02,0.00)	0.00 (-0.01,0.00)	0.14 (-0.08,0.37)	0.00 (0.00,0.00)	0.00 (0.00,0.01)
Ex smoker (v never smoked)	-0.03 (-0.06,0.00)	**-0.07 (-0.13,-0.02)#**	0.00 (-0.03,0.03)	**1.50 (0.26,2.74)#**	0.00 (-0.04,0.03)	**0.04 (0.01,0.07)#**
Current smoking (v never smoked)	-0.03 (-0.08,0.02)	-0.05 (-0.15,0.04)	-0.01 (-0.06,0.04)	0.98 (-1.04,3.00)	-0.01 (-0.06,0.04)	**0.07 (0.02,0.12)#**
Family history of CVD (v no family history)	-0.02 (-0.06,0.01)	-0.02 (-0.08,0.04)	-0.02 (-0.06,0.01)	-0.02 (-1.36,1.33)	-0.02 (-0.06,0.01)	0.01 (-0.03,0.05)

*Test for significance of coefficient: p<0.01, #test for significance of coefficient: p<0.05.
$Proportion of variability (adjusted r^2) explained by the cardiovascular, demographic and blood markers included in model. CI=confidence interval, LV=left ventricular, bpm=beats per minute, BMI=body mass index, BNP=B-type natriuretic peptide, HDL=high density lipoprotein, LDL=low density lipoprotein, SIMD=Scottish index of multiple deprivation, CVD=cardiovascular disease.

Table 4.22: Multivariable analysis of traditional cardiovascular risk factors, socio-demographic factors and BNP in relation to other left ventricular measures in women

	log end diastolic volume (ml)	log end systolic volume (ml)	log stroke volume (ml)	Ejection fraction (%)	log cardiac output (l/min)	log LV mass/LV end diastolic volume (g/ml)
Proportion of variability explained by model$	22.3%	13.3%	20.7	5.3%	42.1%	17.1%
Risk factor coefficient (95% CI)						
log Age (years)	**-0.34 (-0.42,-0.26)***	**-0.51 (-0.67,-0.35)***	**-0.27 (-0.36,-0.19)***	**4.61 (1.29,7.94)***	**-0.28 (-0.36,-0.19)***	**0.16 (0.07,0.24)***
log Heart rate (bpm)	**-0.28 (-0.35,-0.21)***	**-0.30 (-0.44,-0.17)***	**-0.30 (-0.38,-0.23)***	-0.68 (-3.60,2.24)	**0.70 (0.62,0.77)***	**0.08 (0.008,0.15)#**
log Triglycerides (mmol/l)	**-0.04 (-0.07,-0.02)***	**-0.06 (-0.11,-0.01)#**	**-0.04 (-0.07,-0.02)***	0.34 (-0.69,1.37)	**-0.04 (-0.07,-0.02)***	0.02 (-0.01,0.04)
log BMI (kg/m^2)	**0.25 (0.13,0.36)***	0.18 (-0.04,0.40)	**0.28 (0.17,0.40)***	2.38 (-2.27,7.04)	**0.28 (0.17,0.40)***	-0.06 (-0.18,0.05)
log BNP (pg/ml)	0.02 (-0.01,0.04)	0.03 (-0.01,0.08)	0.01 (-0.02,0.03)	-0.68 (-1.67,0.31)	0.01 (-0.02,0.03)	-0.01 (-0.03,0.02)
Systolic BP (mmHg)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	**0.002 (0.001,0.003)***	**0.08 (0.03,0.13)***	**0.002 (0.001,0.003)***	**0.002 (0.00,0.003)***
Diastolic BP (mmHg)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.02 (-0.05,0.08)	0.00 (0.00,0.00)	**0.003 (0.001,0.004)***
HDL (mmol/l)	0.00 (-0.03,0.03)	0.01 (-0.05,0.06)	-0.01 (-0.04,0.02)	-0.25 (-1.41,0.92)	-0.01 (-0.04,0.02)	-0.01 (-0.04,0.02)
LDL (mmol/l)	**-0.01 (-0.03,-0.002)#**	-0.02 (-0.05,0.00)	-0.01 (-0.03,0.00)	0.25 (-0.28,0.78)	-0.01 (-0.03,0.00)	**0.02 (0.01,0.03)***
Waist circumference (cm)	0.00 (0.00,0.00)	0.00 (0.00,0.01)	0.00 (0.00,0.00)	-0.03 (-0.10,0.03)	0.00 (0.00,0.00)	**0.002 (0.001,0.004)***
SIMD Decile	0.00 (0.00,0.01)	0.00 (-0.01,0.01)	0.01 (0.002,0.01)*	0.14 (-0.04,0.31)	**0.01 (0.002,0.01)***	0.00 (0.00,0.01)
Ex smoker (v never smoked)	0.01 (-0.02,0.03)	0.03 (-0.02,0.07)	-0.01 (-0.03,0.02)	-0.75 (-1.77,0.27)	-0.01 (-0.03,0.02)	-0.01 (-0.03,0.02)
Current smoking (v never smoked)	0.02 (-0.02,0.05)	0.05 (-0.02,0.11)	0.00 (-0.04,0.03)	-1.16 (-2.55,0.23)	0.00 (-0.03,0.03)	**0.06 (0.03,0.10)***
Family history of CVD (v no family history)	-0.01 (-0.03,0.02)	-0.02 (-0.07,0.02)	0.00 (-0.03,0.02)	0.42 (-0.55,1.39)	-0.01 (-0.03,0.02)	0.00 (-0.02,0.03)

*Test for significance of coefficient: p<0.01, #test for significance of coefficient: p<0.05.
$Proportion of variability (adjusted r^2) explained by the cardiovascular, demographic and blood markers included in model. CI=confidence interval, LV=left ventricular, bpm=beats per minute, BMI=body mass index, BNP=b-type natriuretic peptide, HDL=high density lipoprotein, LDL=low density lipoprotein, SIMD=Scottish index of multiple deprivation, CVD=cardiovascular disease.

In men stroke volume, end diastolic volume and end systolic volume were independently inversely associated with age and heart rate and positively associated with BMI. End diastolic volume was also weakly inversely associated with LDL. Cardiac output was inversely associated with age and positively associated with heart rate and BMI. LVM/LVEDV was associated with heart rate, ex-smoking status or current smoking status and weakly with SBP. BNP was not independently associated with any of the measures of LV function in men.

In women stroke volume, end diastolic volume and end systolic volume were independently inversely associated with age and heart rate as in men but also with triglyceride level. End diastolic volume and stroke volume (but not end systolic volume as in men) were associated with BMI and stroke volume was weakly associated with systolic blood pressure. As in men LDL was weakly inversely associated with end diastolic volume. Cardiac output was inversely associated with age and positively associated with heart rate and BMI as in men but was also inversely associated with triglycerides and positively weakly associated with systolic blood pressure. LVM/LVEDV was associated with heart rate, current smoking status and systolic blood pressure as in men but not with ex-smoking status. It was additionally associated with diastolic blood pressure (weakly) and LDL level. BNP was not independently associated with any of the measures of LV function in women.

4.4. Whole body MRI angiogram results

4.4.1. Angiogram results

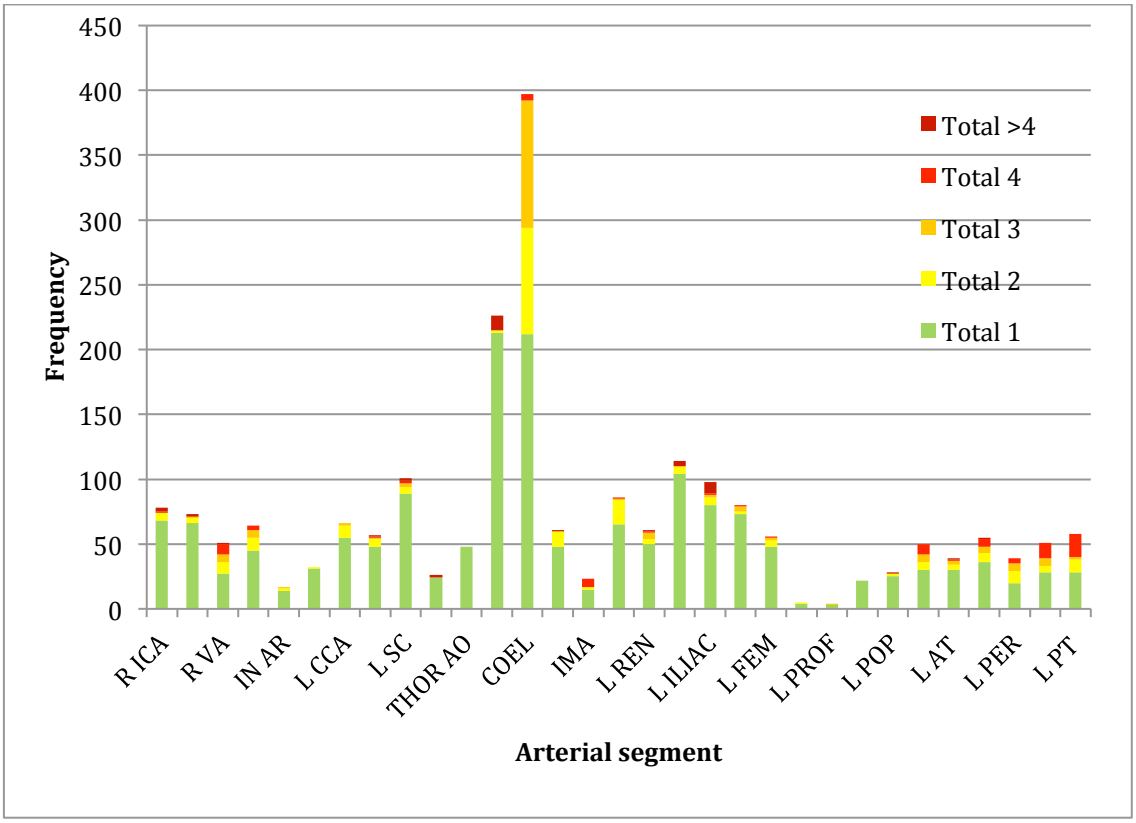
1513 participants had all or some of their arterial tree imaged to allow assessment for arterial luminal stenosis. 1500 also had cardiac imaging available: the remaining 13 had only MRA imaging because either their scan was abandoned partway through or the cardiac images were not suitable for analysis. A breakdown of the number and percentage of arterial segments with various degrees of luminal stenosis and other abnormalities is given in table 4.23 and is illustrated graphically in figure 4.7. The presence and degree of abnormality is given for each of the 31 segments analysed per patient to show the distribution of abnormality. The vast majority of segments (44435, 94.6%) were assessed as normal. Of the vessel segments assessed to have some stenosis or aneurysm most had only a mild stenosis (<50%) however a reasonable number of segments had a more significant stenosis. 40 arterial segments were aneurysmal although only 7 of these were associated with a stenosis. Therefore the majority of contribution towards the standardised atheroma scores (SAS) greater than 0 came from stenosis.

Figure 4.6: Example of bilateral carotid stenoses detected by WB CE-MRA in a 47 year old woman

Table 4.23: Individual arterial segment scores obtained from WB CE-MRA images

	Normal	<50% stenosis	51-70% stenosis	71-99% stenosis	Occlusion	Aneurysm but no stenosis	Aneurysm and <50% stenosis	Aneurysm and 51-70% stenosis	Aneurysm and 71-99% stenosis	Aneurysm and occlusion	Uninterpretable/not imaged
Right Internal Carotid	1435	68	6	0	1	2	0	1	0	0	1
Left Internal Carotid	1439	66	4	1	0	2	0	0	0	0	2
Right Vertebral	1449	27	9	6	8	1	0	0	0	0	14
Left Vertebral	1434	45	10	6	3	0	0	0	0	0	16
Inominate	1482	14	2	1	0	0	0	0	0	0	14
Right Common Carotid	1468	31	1	0	0	0	0	0	0	0	14
Left Common Carotid	1435	55	9	2	0	0	0	0	0	0	13
Right Subclavian	1444	48	6	1	1	0	1	0	0	0	11
Left Subclavian	1388	89	5	3	2	2	0	0	0	0	25
Aortic Arch	1484	24	0	0	0	2	0	0	0	0	3
Thoracic Aorta	1457	48	0	0	0	0	0	0	0	0	9
Abdominal Aorta	1282	213	2	0	0	10	1	0	0	0	5
Coeliac Trunk	1105	212	82	98	5	0	0	0	0	0	11
Superior Mesenteric	1443	48	12	0	0	1	0	0	0	0	9
Inferior Mesenteric	1471	15	2	0	6	0	0	0	0	0	18
Right Renal	1416	65	19	1	1	0	0	0	0	0	11
Left Renal	1439	50	4	5	1	0	1	0	0	0	12
Right Iliac	1392	104	5	1	0	3	1	0	0	0	7
Left Iliac	1408	80	6	2	1	7	2	0	0	0	6
Right Femoral	1409	73	2	4	1	0	0	0	0	0	23
Left Femoral	1435	48	5	2	1	0	0	0	0	0	22
Right Profunda Femoris	1497	4	1	0	0	0	0	0	0	0	10
Left Profunda Femoris	1498	3	0	1	0	0	0	0	0	0	11
Right Popliteal	1486	22	0	0	0	0	0	0	0	0	5
Left Popliteal	1481	25	2	0	0	1	0	0	0	0	4
Right Anterior Tibial	1461	30	6	6	8	0	0	0	0	0	2
Left Anterior Tibial	1472	30	4	3	1	1	0	0	0	0	1
Right Peroneal	1455	36	7	5	6	1	0	0	0	0	3
Left Peroneal	1469	20	9	6	4	0	0	0	0	0	4
Right Posterior Tibial	1454	28	5	6	12	0	0	0	0	0	8
Left Posterior Tibial	1447	28	10	2	18	0	0	0	0	0	8
All segments (total)	**44435**	**1649**	**235**	**162**	**80**	**33**	**6**	**1**	**0**	**0**	**302**

Figure 4.7: Distribution of abnormalities at arterial segment level



1= less than 50% stenosis, 2= 51-70% stenosis, 3=71-99% stenosis, 4= occlusion, >4=presence of aneurysm with or without stenosis. L=left, R=right, ICA=internal carotid artery, VA=vertebral artery, IN AR=innominate artery, CCA=common carotid artery, SC=subclavian artery, AOR A=aortic arch, THOR AO=thoracic aorta, ABDO AO=abdominal aorta, COEL=coeliac trunk, SMA=superior mesenteric artery, IMA=inferior mesenteric artery, REN=renal artery, ILIAC=iliac artery, FEM=femoral artery, PROF=profunda femoris artery, POP=popliteal artery, AT=anterior tibial artery, PER=peroneal artery, PT=posterior tibial artery.

The arterial segment most frequently assessed to have a stenosis was the coeliac trunk. As discussed later it is not clear if apparent stenosis is genuine or an artefact brought about by the anatomy of the artery. Therefore results for the whole body contrast enhanced magnetic resonance angiography (WB CE-MRA) looking at abnormalities in individual participants are presented both with and without the coeliac trunk included.

At an individual participant level the number of segments affected are summarised in figures 4.8 and 4.9. 506 participants had multiple arterial segments (as opposed to a single arterial segment) affected by stenosis suggesting disease in more than one arterial territory.

Figure 4.8: Number of segments affected per individual participant (if coeliac artery included)

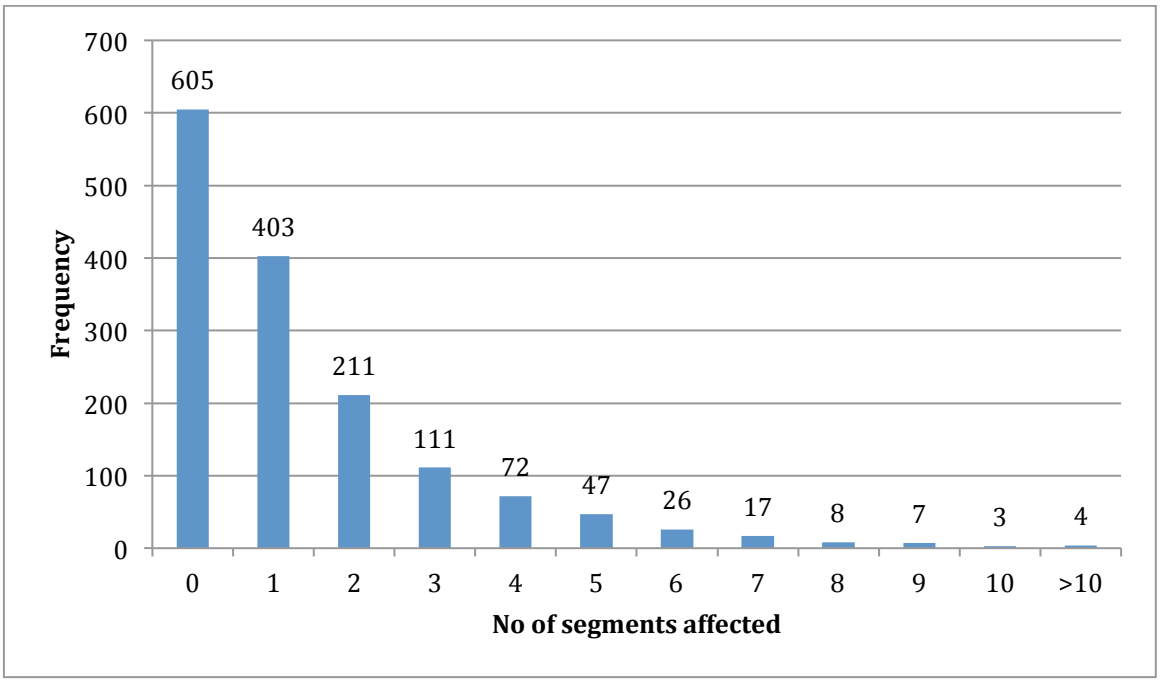
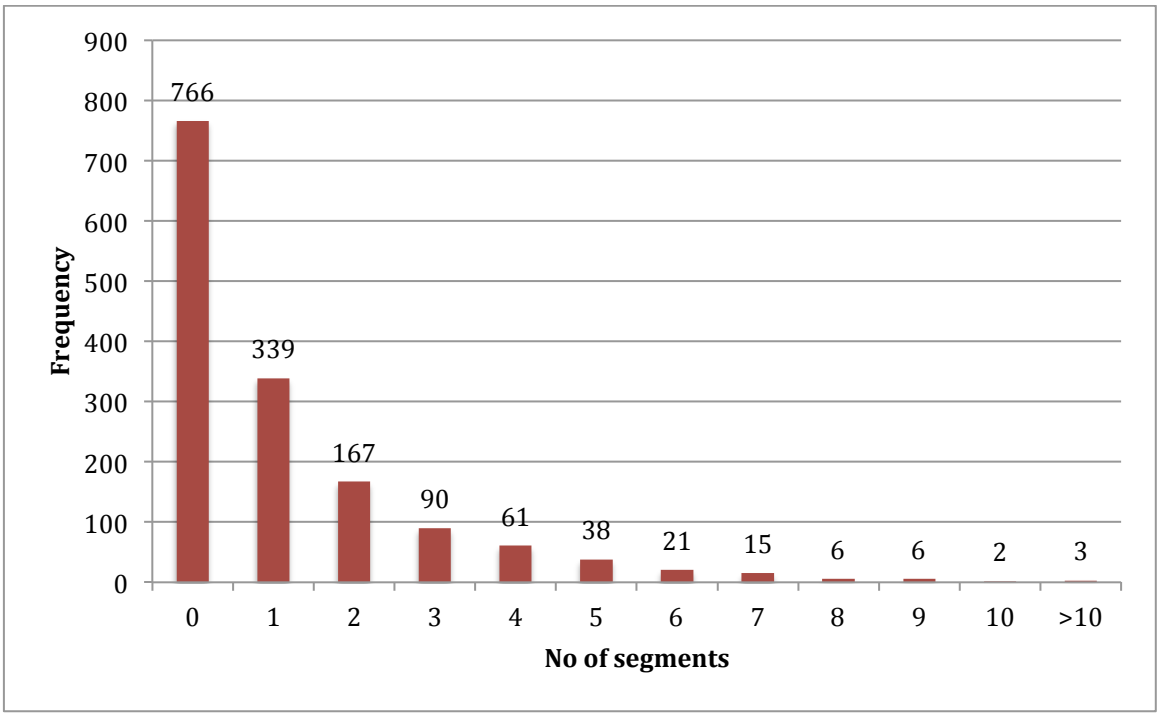


Figure 4.9: Number of segments affected per individual participant (if coeliac artery excluded)



The standardised whole body atheroma scores (SAS) are illustrated in figure 4.10 and demonstrate a marked positive skew. The distribution of regional standardised atheroma scores is illustrated in figure 4.11. Summary values for the whole body and regional standardised atheroma scores are given in table 4.24 and for whole body SAS in men and women separately in table 4.25.

Figure 4.10: Distribution of standardised atheroma scores with coeliac excluded (left) and included (right)

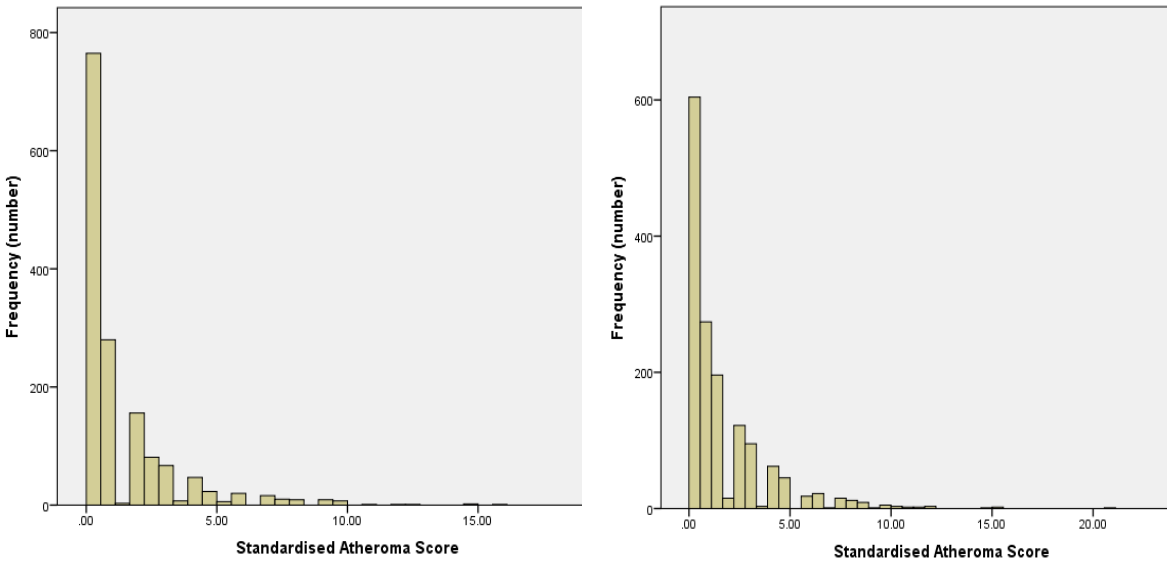
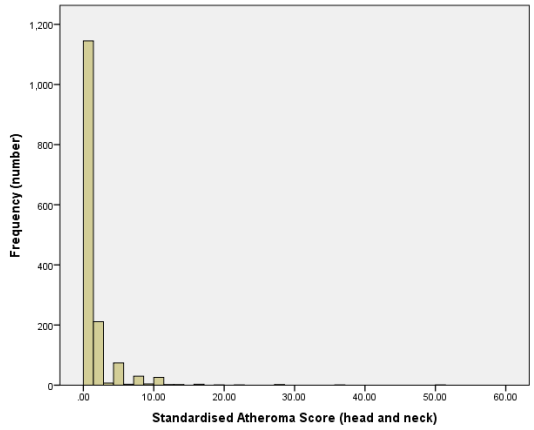
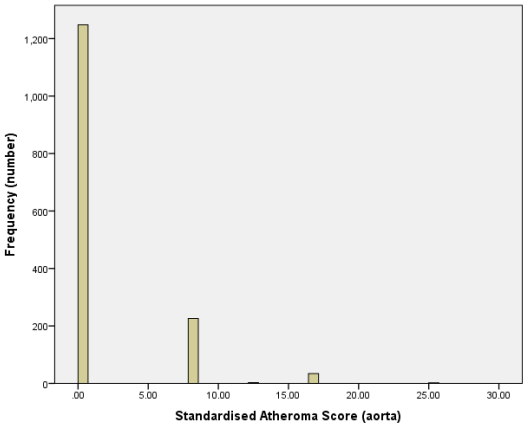
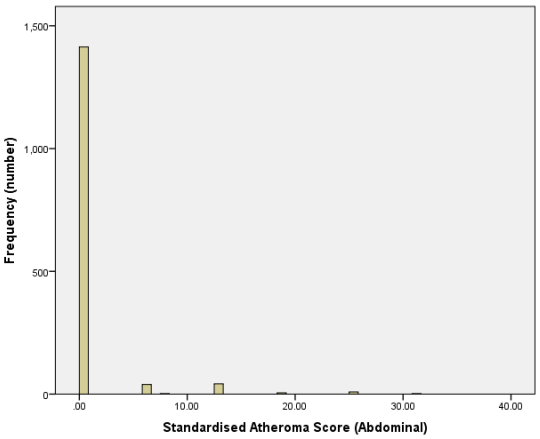
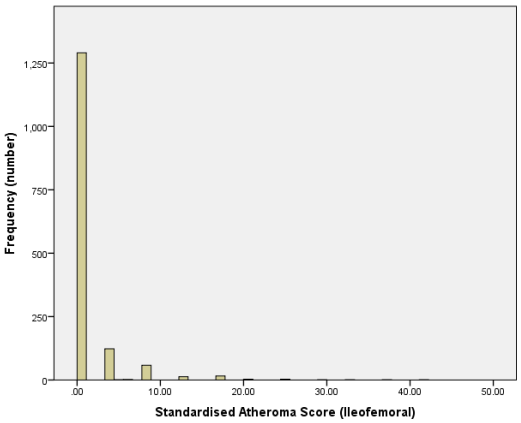


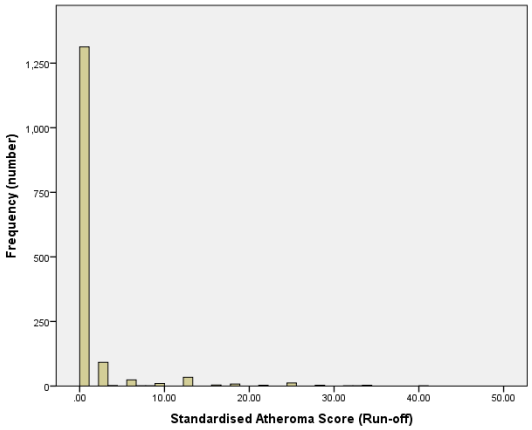
Figure 4.11: Distribution of regional atheroma scores. From top left to bottom right: head and neck, aorta, abdomen, iliofemoral, run-off











Head and neck arteries = right and left internal carotid arteries, right and left common carotid arteries, innominate artery, right and left vertebral arteries, right and left subclavian arteries. Aorta = aortic arch, thoracic aorta, abdominal aorta. Abdominal = coeliac trunk, superior mesenteric artery, inferior mesenteric artery, right and left renal arteries. Ileofemoral = right and left iliac arteries, right and left femoral arteries, right and left profunda femoris. Run off = right and left popliteal arteries, right and left anterior tibial arteries, right and left posterior tibial arteries, right and left peroneal arteries.

Table 4.24: Regional standardised atheroma scores

Region	Median (IQR)	80th percentile	90th percentile
Whole body	0 (1.67)	2.50	4.17
Head and neck	0 (0.0)	2.80	3.96
Aorta	0 (0.0)	0.0	8.3
Abdominal	0 (0.0)	0.0	0.0
Iliofemoral	0 (0.0)	0.0	4.20
Run-off	0 (0.0)	0.0	3.10

IQR=inter-quartile range. Head and neck arteries = right and left internal carotid arteries, right and left common carotid arteries, innominate artery, right and left vertebral arteries, right and left subclavian arteries. Aorta = aortic arch, thoracic aorta, abdominal aorta. Abdominal = coeliac trunk, superior mesenteric artery, inferior mesenteric artery, right and left renal arteries. Ileofemoral = right and left iliac arteries, right and left femoral arteries, right and left profunda femoris. Run off = right and left popliteal arteries, right and left anterior tibial arteries, right and left posterior tibial arteries, right and left peroneal arteries.

Table 4.25: Standardised atheroma scores for men and women

	Men (n=577)	Women (n=936)	p value*
Median	0.00	0.83	0.08
80th percentile	1.67	2.50	-
90th percentile	3.33	4.17	-

*Mann-Whitney test used to look for difference between men and women.

4.4.2. Correlation of angiogram results with risk factors and BNP

The correlations between the whole body standardised atheroma score and the baseline demographic and risk factors were assessed by univariate analysis (table 4.26).

Table 4.26: Univariate analysis of correlations between baseline factors and standardised whole body atheroma score

Variable	Association with SAS		
	Entire population (n=1513)	Men (n=577)	Women (n=936)
Age (years)	**0.25 (<0.001)**	**0.28 (<0.001)**	**0.23 (<0.001)**
Systolic BP (mmHg)	**0.11 (<0.001)**	**0.10 (0.02)**	**0.13 (<0.001)**
Diastolic BP (mmHg)	0.03 (0.19)	0.04 (0.29)	0.04 (0.20)
Heart rate (beats/min)	0.05 (0.05)	0.02 (0.64)	0.06 (0.06)
Total cholesterol (mmol/l)	**0.16 (<0.001)**	**0.13 (0.002)**	**0.17 (<0.001)**
HDL (mmol/l)	0.03 (0.28)	0.00 (0.93)	0.02 (0.49)
LDL (mmol/l)	**0.12 (<0.001)**	**0.10 (0.026)**	**0.14 (<0.001)**
Triglycerides (mmol/l)	**0.06 (0.018)**	0.05 (0.20)	**0.09 (0.007)**
BMI (kg/m^2)	-0.03 (0.26)	0.00 (0.92)	-0.03 (0.31)
Waist circumference (cm)	-0.02 (0.43)	0.05 (0.21)	-0.02 (0.47)
SIMD	**-0.08 (0.005)**	-0.08 (0.06)	-0.01 (0.67)
Predicted CHD risk score using ATPIII algorithm (%/10 years)	**0.15 (<0.001)**	**0.28 (<0.001)**	**0.22 (<0.001)**
BNP (pg/ml)	0.03 (0.20)	0.06 (0.13)	-0.02 (0.64)

Spearman rank correlation test is used. ρ and (p) values are given. SAS=standardised atheroma score, HDL=high density lipoprotein, LDL=low density lipoprotein, BMI=body mass index, BNP=B-type natriuretic peptide, SIMD=Scottish index of multiple deprivation, CHD=coronary heart disease, ATPIII= Adult Treatment Panel III.

Linear multiple regression modelling demonstrated that age, heart rate, systolic BP, SIMD decile, ex-smoking status and current smoking status were independently associated with SAS (table 4.27). The original model included age, gender, smoking status, systolic BP, diastolic BP, heart rate, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, BMI, waist circumference, family history of cardiovascular disease, SIMD decile and BNP level. Those variables with a positively skewed distribution were log transformed to create a near normal distribution.

Table 4.27: Multivariable analysis of traditional cardiovascular risk factors, socio-demographic factors and BNP in relation to standardised atheroma score

Proportion of variability explained by model$	11.4%
Risk factor coefficient (95% CI)	
log age (years)	3.40 (2.61,4.20)*
log heart rate (bpm)	1.23 (0.51,1.95)*
log triglycerides (mmol/l)	0.24 (-0.39,0.87)
log BMI (kg/m^2)	-0.26 (-1.46,0.93)
log BNP (pg/ml)	0.15 (-0.08,0.38)
Systolic BP (mmHg)	0.02 (0.01,0.03)*
Diastolic BP (mmHg)	-0.01 (-0.03,0.01)
Total cholesterol (mmol/l)	-0.12 (-0.95,0.70)
HDL (mmol/l)	-0.01 (-0.87,0.86)
LDL (mmol/l)	0.23 (-0.59,1.04)
Waist circumference (cm)	-0.01 (-0.02,0.01)
SIMD Decile	-0.06 (-0.10,-0.02)*
Male gender (compared to female)	0.05 (-0.25,0.36)
Ex smoker (v never smoked)	0.35 (0.10,0.60)*
Current smoking (v never smoked)	0.79 (0.44,1.15)*
Family history of CVD (v no family history)	0.24 (-0.01,0.49)

*Test for significance of coefficient: $p<0.01$, #test for significance of coefficient: $p<0.05$.
$Proportion of variability (adjusted r^2) explained by the cardiovascular, demographic and blood markers included in model. CI=confidence interval, bpm=beats per minute, BMI=body mass index, BNP=B-type natriuretic peptide, HDL=high density lipoprotein, LDL=low density lipoprotein, SIMD=Scottish index of multiple deprivation, CVD=cardiovascular disease.

Because the SAS is very positively skewed the baseline characteristics of those with a SAS above the 80th percentile are compared with those below the 80th percentile in table 4.28. Men and women with an SAS above the 80th percentile were older had a higher systolic blood pressure and had a higher predicted CHD risk when compared to those with an SAS below the 80th percentile. Additionally men were more likely to be current or ex-smokers and women had a higher total and LDL cholesterol and higher triglycerides. There were no significant differences in BNP levels.

Univariate correlations between percentage of vessels with any abnormality and baseline risk factors are given in table 4.29. Percentage of vessels affected was associated with age, systolic BP, total cholesterol, LDL and predicted CHD risk score in both men and women and additionally (weakly) with heart rate and triglycerides in women.

Baseline variables for those with no evidence of stenosis or aneurysm are compared with those with any presence of abnormality in table 4.30. Presence of any stenosis was associated with older age, higher total and LDL cholesterol and higher predicted CHD risk in both men and women, current or ex-smoking status in men and higher systolic BP in women.

Table 4.28: Baseline variables and BNP comparison between those with standardised atheroma score greater and less than 80th centile

Variable		Total population			Men			Women		
		≤80th centile SAS (n=1278)	>80th centile SAS (n=235)	p value	≤80th centile SAS (n=464)	>80th centile SAS (n=113)	p value	≤80th centile SAS (n=786)	>80th centile SAS (n=150)	p value
Median (IQR) age (years)		52.3 (11.8)	58.9 (12.1)	**<0.001**	51.8 (10.8)	59.9 (10.8)	**<0.001**	53.4 (8.2)	58.8 (8.2)	**<0.001**
No (%) current smokers		125 (9.8)	40 (17.0)	**0.001**	32 (6.9)	19 (16.8)	**0.001**	90 (11.5)	24 (16.0)	0.12
No (%) former smokers		332 (26.0)	78 (33.2)	**0.022**	118 (25.4)	45 (39.8)	**0.003**	205 (26.1)	42 (28.0)	0.61
No (%) never smokers		816 (63.8)	116 (49.4)	**<0.001**	312 (67.2)	49 (43.4)	**<0.001**	488 (62.1)	83 (55.3)	0.13
Mean (SD) systolic BP (mmHg)		122.0 (12.1)	125.3 (12.1)	**<0.001**	124.6 (11.0)	127.2 (10.5)	**0.022**	120.2 (12.4)	124.3 (12.7)	**<0.001**
Mean (SD) diastolic BP (mmHg)		72.7 (9.3)	73.5 (9.0)	0.23	74.9 (8.9)	74.8 (8.4)	0.95	71.3 (9.2)	72.8 (9.2)	0.08
Median (IQR) heart rate (beats/min)		62 (12)	63 (13)	0.40	60 (11)	60 (14)	0.73	65 (10)	65 (9)	0.55
Mean (SD) total cholesterol (mmol/l)		5.43 (0.97)	5.71 (0.94)	**<0.001**	5.38 (0.94)	5.52 (0.78)	0.12	5.46 (1.02)	5.81 (1.02)	**<0.001**
Mean (SD) HDL (mmol/l)		1.44 (0.42)	1.47 (0.44)	0.35	1.24 (0.39)	1.28 (0.38)	0.39	1.56 (0.40)	1.56 (0.44)	0.98
Mean (SD) LDL (mmol/l)		3.36 (0.88)	3.56 (0.84)	**0.001**	3.38 (0.85)	3.50 (0.75)	0.15	3.34 (0.90)	3.59 (0.89)	**0.002**
Median (IQR) triglycerides (mmol/l)$^{\$}$		1.26 (1.00)	1.36 (1.01)	**0.043**	1.50 (1.22)	1.60 (1.19)	0.95	1.11 (0.84)	1.26 (0.92)	**0.002**
Median (IQR) BMI (kg/m^2) $^{\$}$		26.2 (5.2)	26.0 (5.4)	0.50	26.7 (4.41)	26.3 (5.19)	0.59	25.6 (5.5)	25.8 (5.5)	0.89
Median (SD) waist circumference (cm)		86.6 (13.1)	86.6 (11.9)	0.99	92.0 (14.0)	93.0 (14.6)	0.72	81.0 (15.0)	82.3 (15.0)	0.55
Median (IQR) predicted CHD risk score using ATPIII algorithm (%/10 years) $^{\$}$		2 (5)	4 (9)	**<0.001**	6 (6)	10 (5)	**<0.001**	1 (2)	2 (3)	**<0.001**
Median (IQR) BNP (pg/ml) $^{\$}$		22.6 (15.0)	23.3 (18.4)	0.19	15.3 (12.0)	16.6 (12.3)	0.07	26.5 (17.3)	26.6 (19.6)	0.90
No (%) with family history of CV disease		323 (25.3)	66 (28.1)	0.37	108 (23.3)	25	0.79	209 (26.6)	47 (31.3)	0.23
SIMD, Number (%)	1	48 (3.8)	17 (7.2)	0.10	12 (2.6)	8 (7.1)	0.31	35 (4.5)	10 (6.7)	0.41
	2	66 (5.2)	13 (5.5)		21 (4.5)	4 (3.5)		44 (5.6)	10 (6.7)	
	3	80 (6.3)	21 (8.9)		26 (5.6)	10 (8.8)		51 (6.5)	14 (9.3)	
	4	66 (5.2)	10 (4.3)		28 (6.0)	6 (5.3)		37 (4.7)	5 (3.3)	
	5	80 (6.3)	15 (6.4)		29 (6.3)	6 (5.3)		51 (6.5)	9 (6.0)	
	6	143 (11.2)	20 (8.5)		52 (11.2)	13 (11.5)		86 (10.9)	12 (8.0)	
	7	202 (15.8)	45 (19.1)		67 (14.4)	21 (18.6)		126 (16.0)	33 (22.0)	
	8	254 (19.9)	40 (17.0)		98 (21.1)	18 (15.9)		155 (19.7)	23 (15.3)	
	9	231 (18.1)	43 (18.3)		88 (19.0)	20 (17.7)		140 (17.8)	26 (17.3)	
	10	105 (8.2)	11 (4.7)		43 (9.3)	7 (6.2)		58 (7.4)	8 (5.3)	

[Notes for table 4.29]
Unpaired t-test used to compare means for variables with a normal distribution. Mann-Whitney test used for variables with a skewed distribution (indicated by $). SAS=standardised atheroma score, SD=standard deviation, IQR=interquartile range, HDL=high density lipoprotein, LDL=low density lipoprotein, BMI=body mass index, CHD=coronary heart disease. 80th percentiles 1.67 and 2.5 for men and women respectively.

Table 4.29: Univariate correlations between percentage of arterial segments with any degree of stenosis or aneurysm and baseline risk factors

Variable	Association with percentage of vessels affected by stenosis and/or aneurysm		
	Entire population (n=1513)	Men (n=577)	Women (n=936)
Age (years)	**0.26 (<0.001)**	**0.29 (<0.001)**	**0.24 (<0.001)**
Systolic BP (mmHg)	**0.11 (<0.001)**	**0.10 (0.020)**	**0.14 (<0.001)**
Diastolic BP (mmHg)	0.04 (0.17)	0.03 (0.43)	0.05 (0.13)
Heart rate (beats/min)	**0.05 (0.041)**	0.02 (0.67)	**0.07 (0.043)**
Total cholesterol (mmol/l)	**0.16 (<0.001)**	**0.13 (0.001)**	**0.18 (<0.001)**
HDL (mmol/l)	0.03 (0.20)	0.01 (0.82)	0.03 (0.38)
LDL (mmol/l)	**0.13 (<0.001)**	**0.10 (0.027)**	**0.15 (<0.001)**
Triglycerides (mmol/l)	**0.06 (0.012)**	0.06 (0.13)	**0.09 (0.006)**
BMI (kg/m^2)	-0.03 (0.30)	0.003 (0.94)	-0.03 (0.32)
Waist circumference (cm)	-0.02 (0.52)	0.06 (0.16)	-0.02 (0.50)
SIMD	-0.04 (0.11)	-0.08 (0.07)	-0.02 (0.58)
Predicted CHD risk score using ATPIII algorithm (%/10 years)	**0.15 (<0.001)**	**0.29 (<0.001)**	**0.22 (<0.001)**
BNP (pg/ml)	0.04 (0.13)	0.07 (0.09)	-0.01 (0.70)

Spearman rank correlation test is used. ρ and (p) values are given. HDL=high density lipoprotein, LDL=low density lipoprotein, BMI=body mass index, BNP=B-type natriuretic peptide, SIMD=Scottish index of multiple deprivation, CHD=coronary heart disease, ATPIII= Adult Treatment Panel III.

Table 4.30: Comparison of baseline characteristics between those with no atheroma and those with any atheroma

		Total population			Men			Women		
Variable		No stenosis (n=765)	Any stenosis (n=748)	p value*	No stenosis (n=308)	Any stenosis (n=269)	p value*	No stenosis (n=457)	Any stenosis (n=479)	p value*
Median (IQR) age (years)		51.7 (11.6)	55.3 (13.0)	**<0.001**	51.5 (10.3)	55.6 (13.5)	**<0.001**	51.9 (12.3)	55.3 (12.9)	**<0.001**
No (%) current smokers		68 (8.9)	97 (13.0)	**0.010**	20 (6.5)	31 (11.5)	**0.034**	48 (10.5)	66 (13.8)	0.12
No (%) former smokers		199 (26.0)	211 (28.2)	0.32	76 (24.7)	87 (32.3)	**0.041**	123 (26.9)	124 (25.9)	0.75
No (%) never smokers		496 (64.8)	436 (58.3)	**0.011**	211 (68.5)	150 (55.8)	**0.002**	285 (62.4)	286 (59.7)	0.45
Mean (SD) systolic BP(mmHg)		121.6 (12.3)	123.4 (11.9)	**0.006**	124.6 (11.3)	125.8 (10.5)	0.17	119.7 (12.5)	122.0 (12.4)	**0.005**
Mean (SD) diastolic BP(mmHg)		72.6 (9.4)	73.0 (9.0)	0.36	74.5 (9.1)	75.2 (8.5)	0.36	71.3 (9.4)	71.8 (9.0)	0.38
Median (IQR) heart rate (bpm)		61 (11)	63 (11)	0.08	60 (12)	61 (12)	0.51	63 (10)	64 (12)	0.14
Mean (SD) total cholesterol (mmol/L)		5.33 (0.93)	5.62 (1.00)	**<0.001**	5.31 (0.91)	5.52 (0.91)	**0.006**	5.35 (0.94)	5.67 (1.04)	**<0.001**
Mean (SD) high density lipoprotein (mmol/l)		1.43 (0.42)	1.45 (0.43)	0.25	1.26 (0.39)	1.24 (0.38)	0.61	1.54 (0.40)	1.57 (0.41)	0.27
Mean (SD) low density lipoprotein (mmol/l)		3.28 (0.85)	3.49 (0.89)	**<0.001**	3.33 (0.84)	3.48 (0.82)	**0.040**	3.25 (0.85)	3.51 (0.93)	**<0.001**
Median (IQR) triglycerides (mmol/l)		1.25 (1.00)	1.30 (1.02)	0.12	1.48 (1.19)	1.60 (1.24)	0.15	1.11 (0.86)	1.17 (0.86)	0.15
Median (IQR) body mass index (kg/m^2)		26.4 (5.3)	26.0 (5.1)	0.16	26.7 (4.3)	26.7 (4.7)	0.80	25.7 (6.0)	25.5 (5.4)	0.10
Mean (SD) waist circumference (cm)		86.9 (13.2)	86.3 (12.6)	0.40	92.0 (11.8)	93.3 (11.0)	0.17	83.4 (13.0)	82.4 (11.7)	0.21
Median (IQR) 10 year CHD risk estimation (%)		2 (4)	2 (5)	**<0.001**	6 (6)	8 (7)	**<0.001**	1 (2)	1↑ (2)	**<0.001**
No (%) with family history of CV disease		188 (24.6)	201 (26.9)	0.31	69 (22.4)	64 (23.8)	0.69	119 (26.0)	137 (28.6)	0.38
SIMD, Number (%)	1	31 (4.1)	34 (4.5)	0.65	8 (2.6)	12 (4.5)	0.31	23 (5.0)	22 (4.6)	0.87
	2	37 (4.8)	42 (5.6)		12 (3.9)	13 (4.8)		25 (5.5)	29 (6.1)	
	3	55 (7.2)	46 (6.1)		20 (6.5)	16 (5.9)		35 (7.7)	30 (6.3)	
	4	37 (4.8)	39 (5.2)		18 (5.8)	16 (5.9)		19 (4.2)	23 (4.8)	
	5	46 (6.0)	49 (6.6)		19 (6.2)	16 (5.9)		27 (5.9)	33 (6.9)	
	6	90 (11.8)	73 (9.8)		38 (12.3)	27 (10.0)		52 (11.4)	46 (9.6)	
	7	113 (14.8)	134 (17.9)		36 (11.7)	52 (19.3)		77 (16.8)	82 (17.1)	
	8	151 (19.7)	143 (19.1)		63 (20.5)	53 (19.7)		88 (19.3)	90 (18.8)	
	9	145 (19.0)	129 (17.2)		63 (20.5)	45 (16.7)		82 (17.9)	84 (17.5)	
	10	57 (7.5)	59 (7.9)		31 (10.1)	19 (7.1)		26 (5.7)	40 (8.4)	

*Unpaired t-test was used for normally distributed variables, Mann-Whitney test for skewed and ranked variables and Chi-square test for categorical variables. SIMD was treated as a continuous variable for the purpose of analysis. SD=standard deviation, IQR=inter-quartile range, bpm=beats per minute, CHD=coronary heart disease, BP=blood pressure, SIMD=Scottish Index of Multiple Deprivation.

BNP levels in men and women with and without arterial abnormality are shown in table 4.31. There was no significant difference in BNP level between those with and without stenosis.

Table 4.31: BNP levels in men and women with and without arterial abnormality on MRA

	Median (IQR) of BNP pg/ml		
	No stenosis	Presence of any stenosis	p value*
Men	15.2 (11.70)	16.1 (11.65)	0.31
Women	26.7 (17.40)	26.2 (17.70)	0.59

*comparison is between those with and without stenosis using Mann-Whitney test. BNP=B-type natriuretic peptide. IQR=inter-quartile range.

4.4.3. Correlation of angiogram results with left ventricular measures

The assessment of correlation between the standardised atheroma score (SAS) and left ventricular measures and between the percentage of vessels affected and left ventricular measures are summarised in tables 4.32 and 4.33 respectively. Only cases where both angiogram and cardiac imaging data were available were included in the analysis. End systolic and diastolic volumes and stroke volume were weakly inversely associated with both SAS and percentage of vessels affected, and LVM/LVEDV was weakly positively associated with both SAS and the percentage of vessels affected in both men and women. Ejection fraction was very weakly associated with SAS in women and percentage of vessels affected in both men and women. LVM indexed for height$^{2.7}$ was associated with SAS and percentage of vessels affected in men.

Table 4.32: Univariate correlations between standardised atheroma score and left ventricular measures

Left ventricular measure	Men (n=572)		Women (n=928)	
	ρ	p	ρ	p
LV mass (g)	0.04	0.30	-0.06	0.08
LVMI (height) (g/m)	0.06	0.15	-0.04	0.19
LVMI (height$^{1.7}$) (g/m$^{1.7}$)	0.07	0.09	-0.03	0.37
LVMI (height$^{2.7}$) (g/m$^{2.7}$)	**0.09**	**0.040**	-0.01	0.77
LVMI (BSA using dubois formula) (g/m^2)	0.06	0.12	-0.02	0.63
LVMI (BSA using Mosteller fornula) (g/m^2)	0.06	0.14	-0.01	0.71
LV end diastolic volume (ml)	**-0.12**	**0.003**	**-0.15**	**<0.001**
LV end systolic volume (ml)	**-0.12**	**0.004**	**-0.14**	**<0.001**
LVM/LVEDV (g/ml)	**0.16**	**<0.001**	**0.09**	**0.005**
Ejection fraction (%)	0.08	0.06	**0.07**	**0.024**
Stroke volume (ml)	**-0. 9**	**0.030**	**-0.13**	**<0.001**
Cardiac output (l/min)	-0.07	0.09	-0.02	0.48

Spearman rank correlation test was used. LV=left ventricular, LVM=left ventricular mass, LVMI=left ventricular mass index, LVEDV=left ventricular end diastolic volume, SAS=standardised atheroma score.

Table 4.33: Univariate correlations between percentage of arterial segments affected and left ventricular measures

Left ventricular measure	Men (n=572)		Women (n=928)	
	ρ	p	ρ	p
LV mass (g)	0.04	0.40	-0.06	0.06
LVMI (height) (g/m)	0.05	0.20	-0.05	0.15
LVMI (height$^{1.7}$) (g/m$^{1.7}$)	0.07	0.11	-0.03	0.31
LVMI (height$^{2.7}$) (g/m$^{2.7}$)	**0.08**	**0.044**	-0.01	0.69
LVMI (BSA using dubois formula) (g/m^2)	0.06	0.18	-0.02	0.56
LVMI (BSA using Mosteller fornula) (g/m^2)	0.05	0.20	-0.02	0.64
LV end diastolic volume (ml)	**-0.12**	**0.004**	**-0.16**	**<0.001**
LV end systolic volume (ml)	**-0.12**	**0.004**	**-0.14**	**<0.001**
LVM/LVEDV (g/ml)	**0.15**	**<0.001**	**0.09**	**0.004**
Ejection fraction (%)	**0.08**	**0.049**	**0.07**	**0.024**
Stroke volume (ml)	**-0.09**	**0.040**	**-0.13**	**<0.001**
Cardiac output (l/min)	-0.07	0.10	-0.03	0.45

Spearman rank correlation test was used. LV=left ventricular, LVM=left ventricular mass, LVMI=left ventricular mass index, LVEDV=left ventricular end diastolic volume, SAS=standardised atheroma score.

Because SAS is very positively skewed and the vast majority of participants have a score of zero LV measures in those above and below the 80th centile are compared in table 4.34 and between those with and without any arterial abnormality in table 4.35. An SAS >80th percentile was associated with lower end systolic end diastolic and stroke volumes and higher LVM/LVEDV in both men and women and with a slightly higher ejection fraction in women. Presence of any stenosis is associated with higher end systolic volume and LVM/LVEDV in both men and women and with lower end diastolic and stroke volumes and slightly higher ejection fraction in women.

Table 4.34: Comparison of left ventricular measures in those with standardised atheroma scores above and below 80th centile

Left ventricular measure	Men			Women		
	≤80th centile SAS (n=460)	>80th centile SAS (n=112)	p value*	≤80th centile SAS (n=778)	>80th centile SAS (n=150)	p value*
Mean (SD) LV mass (g)	129.2 (24.4)	129.5 (24.4)	0.91	87.2 (16.5)	86.8 (18.0)	0.92
Mean (SD) LVMI (height) (g/m)	73.1 (13.2)	73.8 (12.9)	0.64	53.4 (9.7)	53.9 (10.4)	0.63
Mean (SD) LVMI (height$^{1.7}$) (g/m$^{1.7}$)	49.1 (8.8)	49.9 (8.5)	0.41	38.0 (6.9)	38.6 (7.2)	0.36
Mean (SD) LVMI (height$^{2.7}$) (g/m$^{2.7}$)	27.9 (5.1)	28.6 (4.8)	0.19	23.4 (4.4)	24.0 (4.4)	0.13
Mean (SD) LVMI (BSA using dubois formula) (g/m^2)	64.1 (10.7)	65.2 (10.3)	0.32	49.3 (8.0)	50.0 (8.3)	0.35
Mean (SD) LVMI (BSA using Mosteller fornula) (g/m^2)	63.6 (10.5)	64.7 (10.1)	0.32	48.8 (7.9)	49.4 (8.3)	0.37
Mean (SD) LV end diastolic volume (ml)	156.5 (26.4)	148.3 (31.8)	**0.005**	120.8 (20.8)	113.7 (21.8)	**<0.001**
Mean (SD) LV end systolic volume (ml)	50.9 (14.4)	47.1 (16.4)	**0.028**	37.8 (12.0)	34.2 (12.2)	**0.001**
Mean (SD) LVM/LVEDV (g/ml)	0.84 (0.14)	0.90 (0.20)	**<0.001**	0.73 (0.12)	0.78 (0.16)	**<0.001**
Mean (SD) Ejection fraction (%)	67.7 (6.2)	68.6 (6.1)	0.16	69.1 (6.5)	70.3 (7.0)	**0.044**
Mean (SD) Stroke volume (ml)	105.6 (18.5)	101.1 (20.4)	**0.036**	83.0 (14.0)	79.5 (14.9)	**0.009**
Mean (SD) cardiac output (l/min)	6.51 (1.17)	6.25 (1.26)	0.05	5.48 (1.09)	5.41 (1.21)	0.55

*comparison was with independent samples t-test. LV=left ventricular, LVM=left ventricular mass, LVMI=left ventricular mass index, LVEDV=left ventricular end diastolic volume, SAS=standardised atheroma score, SD=standard deviation, IQR=inter-quartile range.

Table 4.35: Comparison of left ventricular measures between those with and without any abnormality on whole body angiography

Left ventricular measure	Men			Women		
	No stenosis (n=304)	Presence of any stenosis (n=268)	p value*	No stenosis (n=454)	Presence of any stenosis (n=474)	p value*
Mean (SD) LV mass (g)	128.7 (24.2)	129.9 (24.5)	0.55	88.2 (17.6)	85.8 (15.8)	0.027
Mean (SD) LVMI (height) (g/m)	72.8 (13.2)	73.7 (13.0)	0.41	54.1 (10.4)	52.9 (9.3)	0.07
Mean (SD) LVMI (height$^{1.7}$) (g/m$^{1.7}$)	48.9 (8.8)	49.7 (8.6)	0.31	38.4 (7.4)	37.8 (6.6)	0.15
Mean (SD) LVMI (height$^{2.7}$) (g/m$^{2.7}$)	27.8 (5.1)	28.3 (4.9)	0.20	23.6 (4.6)	23.4 (4.2)	0.39
Mean (SD) LVMI (BSA using dubois formula) (g/m^2)	64.1 (11.0)	64.6 (9.9)	0.56	49.7 (8.4)	48.7 (7.6)	0.41
Mean (SD) LVMI (BSA using Mosteller fornula) (g/m^2)	63.6 (11.0)	64.1 (9.9)	0.60	49.1 (8.3)	48.7 (7.6)	0.48
Mean (SD) LV end diastolic volume (ml)	157.0 (26.3)	152.5 (29.1)	0.05	122.8 (20.7)	116.6 (21.0)	**<0.001**
Mean (SD) LV end systolic volume (ml)	51.3 (14.3)	48.8 (15.4)	**0.046**	38.7 (12.1)	35.8 (11.9)	**<0.001**
Mean (SD) LVM/LVEDV (g/ml)	0.83 (0.14)	0.87 (0.17)	**0.003**	0.73 (0.12)	0.75 (0.14)	**0.010**
Mean (SD) Ejection fraction (%)	67.5 (6.1)	68.3 (6.4)	0.15	68.8 (6.7)	69.8 (6.5)	**0.020**
Mean (SD) Stroke volume (ml)	105.6 (18.3)	103.6 (19.6)	0.20	84.1 (14.4)	80.9 (13.8)	**0.001**
Mean (SD) cardiac output (l/min)	6.48 (1.14)	6.42 (1.25)	0.58	5.48 (1.11)	5.45 (1.12)	0.68

*comparison was with independent samples t-test. LV=left ventricular, LVM=left ventricular mass, LVMI=left ventricular mass index, LVEDV=left ventricular end diastolic volume, SAS=standardised atheroma score, SD=standard deviation, IQR=inter-quartile range.

4.5. MRI angiogram reproducibility

4.5.1. Inter-observer reproducibility

1488 arterial segments were evaluated (n=31 anatomical locations for n=48 volunteers). A full breakdown of the individual arterial segments where disease was noted by consensus is summarised in table 4.36. In 53 (3.6%) segments (involving n=29 of the 48 volunteers) there was some evidence of luminal stenosis. Of these 53 segments, 34 were coded as 1 (minor stenosis 1-50%), 5 were coded as 2 (moderate stenosis 51-70%), 11 were coded as 3 (severe stenosis 70-99%) and 3 cases were coded as 4 (vessel occlusion). However the vast majority of segments were interpreted as radiologically normal.

The greatest frequency of stenosis was recorded at the coeliac trunk, where a stenosis score of 1 or more was noted in n=18 of the volunteers. This was followed by the abdominal aorta (10 cases), and the right and left iliac arteries (4 cases each). At all other segments, some degree of luminal narrowing was only ever noted in n=2 (or less) of the 48 volunteers.

Independent single assessments of all n=48 volunteer datasets by each observer resulted in identical scoring between all four observers in 1277 (85.8%) of the 1488 arterial segments evaluated. Of those that were not scored identically, clear consensus agreement between three out of the four radiologists was recorded for 162 (10.9%) of the segments. Radiological opinion was divided at the remaining 49 segments - which represented 3.3% of the total reviewed. Fleiss' kappa values are listed for each of the arterial segments under investigation as a measure of inter-observer agreement. The worst case agreement was found at the coeliac trunk (k=0.66) and best case perfect agreement was found at the innominate and left popliteal arteries (k=1.00).

The median total whole body atheroma (WBA) score by consensus was 0.8%, and ranged from 0% to 5.6%. When the scores were evaluated between observers (using the Kruskal Wallis test), there was no significant difference detected between the means of those provided by each observer (p=0.14).

Table 4.36: Number of abnormal arterial assessments within the cohort (from a possible n=48 for each location) identified by a consensus of four observers with cardiovascular MRI experience

Arterial Segment	Grade 1	Grade 2	Grade 3	Grade 4	Total (percent)	Fleiss' kappa
R Int. Carotid	0	0	0	0	0	0.89
L Int. Carotid	2	0	0	0	2 (4.2%)	0.90
R Vertebral	0	0	0	0	0 (0%)	0.97
L Vertebral	0	0	0	0	0 (0%)	0.94
Aortic Arch	0	0	0	0	0 (0%)	0.99
Inominate	0	0	0	0	0 (0%)	1.00
R Com. Carotid	0	0	0	0	0 (0%)	0.99
L Com. Carotid	1	0	0	0	1 (2.1%)	0.93
R Subclavian	2	0	0	0	2 (4.2%)	0.88
L Subclavian	0	0	0	0	0 (0%)	0.90
Thoracic Aorta	1	0	0	0	1 (2.1%)	0.86
Abdominal Aorta	10	0	0	0	10 (21.0%)	0.81
Coeliac Trunk	6	5	6	1	18 (37.5%)	0.66
Sup. Mesenteric	1	0	0	0	1 (2.1%)	0.88
Inf. Mesenteric	0	0	1	0	1 (2.1%)	0.91
R Renal	1	0	0	0	1 (2.1%)	0.93
L Renal	0	0	0	0	0 (0%)	0.94
R Iliac	4	0	0	0	4 (8.4%)	0.90
L Iliac	3	0	1	0	4 (8.4%)	0.87
R Femoral	1	0	0	0	1 (2.1%)	0.91
L Femoral	2	0	0	0	2 (4.2%)	0.91
R Profundus	0	0	0	0	0 (0%)	0.96
L Profundus	0	0	0	0	0 (0%)	0.99
R Popliteal	0	0	0	0	0 (0%)	0.97
L Popliteal	0	0	0	0	0 (0%)	1.00
R Ant. Tibial	0	0	0	0	0 (0%)	0.93
L Ant. Tibial	0	0	0	0	0 (0%)	0.97
R Peroneal	0	0	1	0	1 (2.1%)	0.96
L Peroneal	0	0	2	0	2 (4.2%)	0.95
R Post. Tibial	0	0	0	1	1 (2.1%)	0.96
L Post. Tibial	0	0	0	1	1 (2.1%)	0.93

R=right, L=left, Int=Internal, Com=common, Sup=superior, Inf=inferior, Ant=anterior, Post=posterior. Inter-observer agreement for each site is described by Fleiss' kappa statistic.

4.5.2. Intra-observer reproducibility

Intra-observer reproducibility (derived from four equal subsets of n=12 volunteers) resulted in observers 1 and 2 achieving consistent scoring in 356 (95.7%) of 372 arterial segments. For observers 3 and 4, consistent scoring was achieved in 346 (93.0%) and 350 (94.1%) of the segments respectively.

When the WBA scores were compared on a per-observer basis (using the Wilcoxon signed rank test), there was no significant difference between the means of the first and second assessments ($p=0.74$, $p=0.64$, $p=0.71$, and $p=0.71$ for observers 1-4 respectively).

5. Results part 3 – 2-year follow up

5.1. CVD endpoints in eligible population

Follow up data was extracted by the Health Informatics Centre, University of Dundee (HIC) 2 years following the end of recruitment. The data obtained gave follow up for a total of 18,364 person years at risk (9570 and 8794 years for the BNP and MRI/BNP groups respectively). The mean years at risk per person were 4.03 and 4.30 for the BNP and MRI/BNP groups respectively. 33 CV events of interest and 1 death occurred in the eligible population of the study. 17 events and 0 deaths were in the BNP group and 16 events and 1 death were in the MRI/BNP group. The details of the events are summarised in table 5.1. The death in the MRI/BNP group was due to acute myocardial infarction, unspecified (ICD code I21.9). No peripheral arterial disease events or diagnoses were recorded in any of the eligible participants at 2 year follow up.

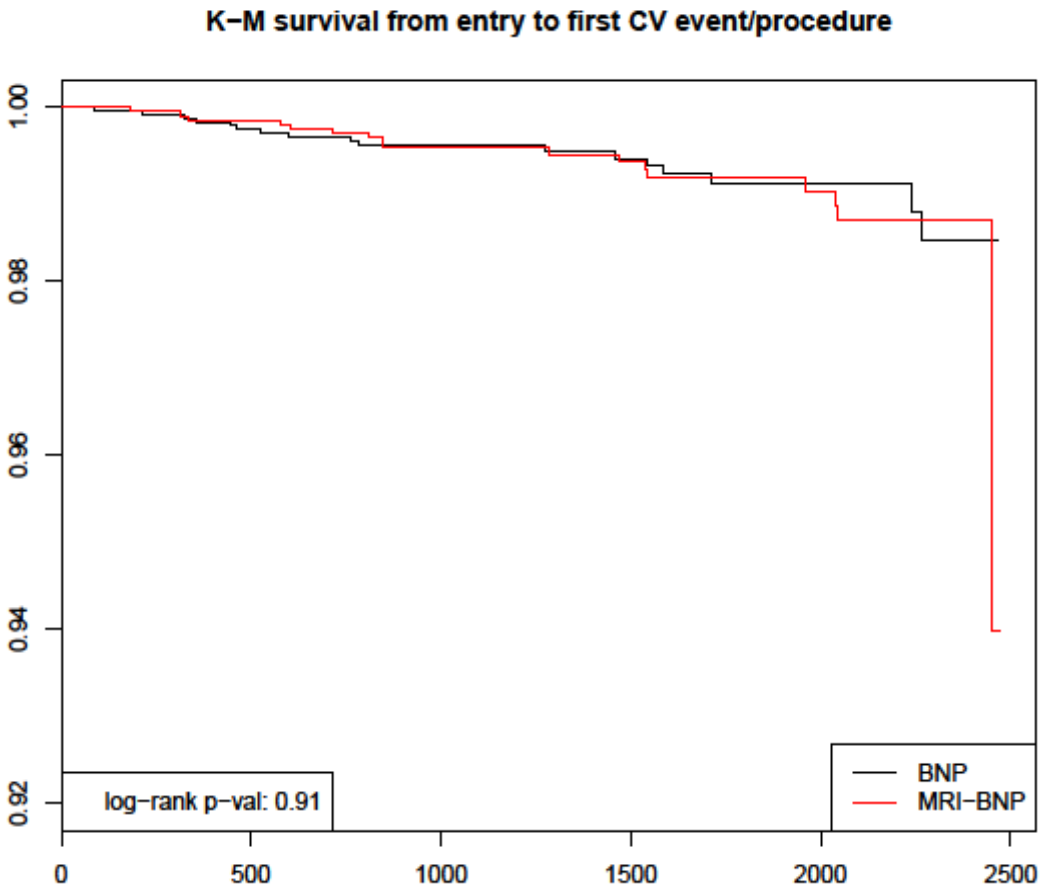
Survival from events in the BNP and MRI/BNP groups is illustrated in the Kaplan-Meier plot (figure 5.1). There was no significant difference in event rates between the BNP and MRI/BNP groups. The CV event rate (95% confidence interval) was 1.85 (1.28-2.59), 1.78 (1.03-2.84) and 1.93 (1.13-3.10) per thousand person-years in the entire eligible population, BNP group and MRI/BNP group respectively.

Table 5.1: Cardiovascular events in the eligible population at 2 year follow up (following end of recruitment)

Diagnosis or procedure	Frequency	
	BNP group (n=2376)	MRI/BNP group (n=2047)
Angina (ICD I20)	5	4
Acute myocardial infarction (ICD I21)	9	5
Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery (OPCS K75.1)	1	1
Cerebral infarction, unspecified (ICD I63.9)	1	2
Intracerebral haemorrhage (ICD I61)	0	1
Stroke not specified as haemorrhage or infarction (ICD I64)	1	3
Total coronary events/procedures	**15**	**10**
Total cerebral events	**2**	**6**
Total events	**17**	**16**

ICD = International Classification of Diseases, OPCS = Office of Population, Censuses and Surveys Classification.

Figure 5.1: Kaplan-Meier plot of survival to first cardiovascular event/procedure



Of the 17 events (16 admissions and 1 death) that occurred in the MRI/BNP group 7 were in participants who had CMR images available. The other 10 were in people who had either not completed an MRI scan or declined a scan. The event rates in those who had CMR images and those who did not were 1.10 (95% CI 0.44-2.26) and 4.15 (2.0-7.6) events per 1000 patient years. The event rates in those with LVM, LVMI and LVM/LVEDV ratios in the upper and lower quartiles for their gender are shown in table 5.2 and between those with LVM, LVMI and LVM/LVEDV ratios above and below the median for their gender in table 5.3. The event rates in those who had an SAS greater than 0 and those who had a score of 0 were 0.65 (95% confidence interval 0.08-2.35) and 1.52 (95% confidence interval 0.49-3.55) respectively.

Table 5.2: Combined cardiovascular event and all-cause mortality rates in those with upper and lower gender specific quartiles of LVM, LVMI and LVM/LVEDV

Cardiac measure	Event rate (95% CI) (Events/1000 participant years)		Number of events	
	Lower quartile for gender	Upper quartile for gender	Lower quartile for gender	Upper quartile for gender
Left ventricular mass	0.64 (0.02-3.56)	1.19 (0.14-4.31)	1	2
Left ventricular mass (corrected for height)	0.63 (0.02-3.54)	1.19 (0.14-4.30)	1	2
Left ventricular mass (corrected for height$^{1.7}$)	0 (0-2.38)	1.20 (0.14-4.32)	0	2
Left ventricular mass (corrected for height$^{2.7}$)	0 (0-2.39)	1.20 (0.15-4.33)	0	2
Left ventricular mass (corrected for body surface area using Dubois formula)	0.65 (0.02-3.65)	1.16 (0.14-4.19)	1	2
Left ventricular mass (corrected for body surface area using Mosteller formula)	0.65 (0.02-3.65)	0.58 (0.01-3.22)	1	1
Left ventricular mass/left ventricular end diastolic volume	0.67 (0.02-3.71)	1.17 (0.14-4.24)	1	2

CI=confidence interval.

Table 5.3: Combined cardiovascular event and all-cause mortality rates in those with LVM, LVMI and LVM/LVEDV above and below gender specific median

Cardiac measure	Event rate (95% CI) (Events/1000 participant years)		Number of events	
	Below median for gender	Above median for gender	Below median for gender	Above median for gender
Left ventricular mass	1.61 (0.52-3.75)	0.61 (0.07-2.21)	5	2
Left ventricular mass (corrected for height)	0.61 (0.07-2.21)	1.61 (0.52-3.75)	2	5
Left ventricular mass (corrected for height$^{1.7}$)	0.96 (0.20-2.80)	1.24 (0.34-3.16)	3	4
Left ventricular mass (corrected for height$^{2.7}$)	0.95 (0.20-2.77)	1.25 (0.34-3.20)	3	4
Left ventricular mass (corrected for body surface area using Dubois formula)	1.29 (0.35-3.31)	0.91 (0.19-2.66)	4	3
Left ventricular mass (corrected for body surface area using Mosteller formula)	1.29 (0.35-3.31)	0.91 (0.19-2.67)	4	3
Left ventricular mass/left ventricular end diastolic volume	0.64 (0.08-2.32)	1.53 (0.50-3.56)	2	5

CI=confidence interval.

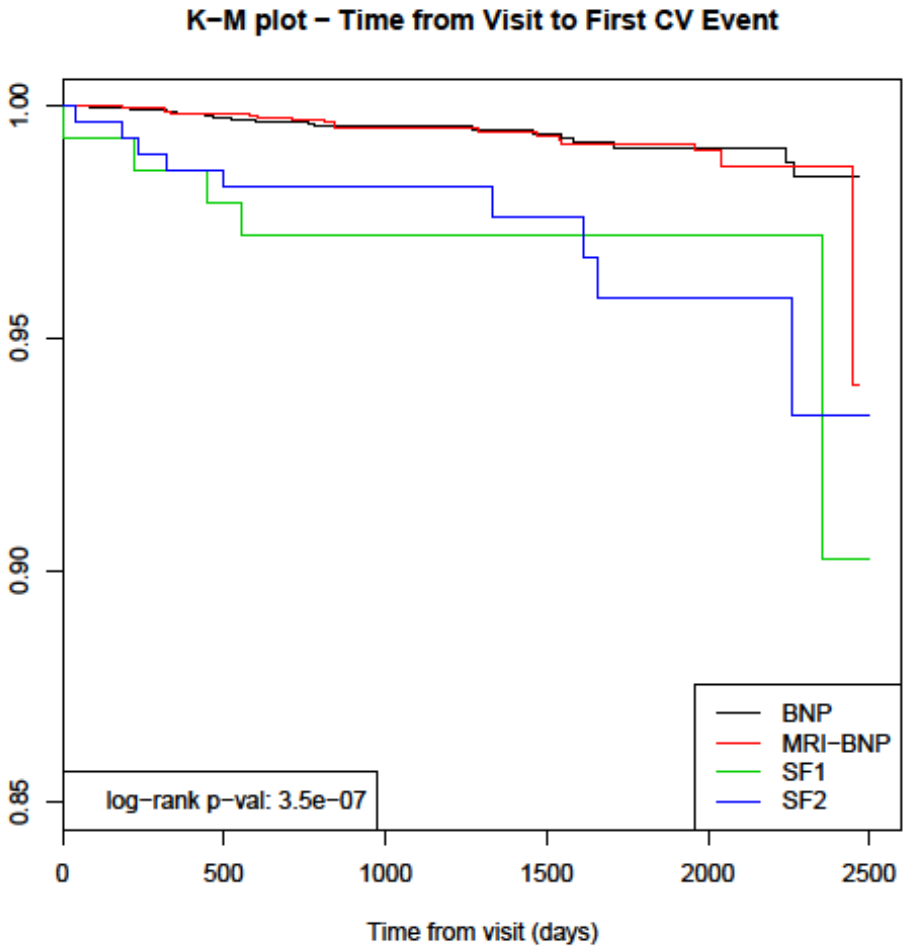
5.2. CVD endpoints in screen fail population

In the data obtained following the end of recruitment, total follow up was 1658 person-years for those who failed screening due to hypertension, dyslipidaemia or high predicted CHD risk. 14 CV events of interest and 2 deaths occurred. 8 CV events and both deaths occurred in those who failed due to hypertension and 6 events and no deaths occurred in those who failed due to high predicted cardiovascular risk. The details of the events are summarised in table 5.4. One of the deaths in the hypertensive group was due to acute myocardial infarction and the other cannot be determined yet due to a lag in the detailed data being obtained from the general registrar office. The CV event rate was 8.4 (95% confidence interval 4.6-14.2) events per 1000 person-years. The death rate was 1.2 (95% confidence interval 0.14-4.2) deaths per 1000 person-years. Survival to events or death comparing the population who failed screening due to high cardiovascular with those who failed screening due to hypertension and the eligible population is shown in the Kaplan-Meier plot (figure 5.2).

Table 5.4: CV events in the population who failed screening due to high cardiovascular risk or hypertension at 2 year follow up

Diagnosis or procedure	Frequency	
	Hypertensive group (n=291)	High CHD risk group (n=146)
Angina (ICD I20)	2	0
Acute myocardial infarction (ICD I21)	3	4
Other forms of acute ischaemic heart disease (ICD I24.8)	1	0
Atherosclerotic heart disease (ICD I25.1)	1	0
Percutaneous transluminal balloon angioplasty of one coronary artery (OPCS K49.1)	1	0
Cerebral infarction, unspecified (ICD I63.9)	0	2
Total coronary events/procedures	**8**	**4**
Total cerebral events	**0**	**2**
Total events	**8**	**6**

Figure 5.2: Kaplan-Meier plot of survival from CV events or all-cause death for those who failed screening due to high predicted cardiovascular risk, those who failed due to hypertension and the eligible study population



BNP=BNP group, MRI/BNP=MRI/BNP group, SF1=failed screening due to high predicted CHD risk, SF2=failed screening due to hypertension.

5.3. Prescribing changes following screening

Medication prescribed before screening visit

145 (33.1%) of the participants who failed screening due to high CHD risk or hypertension had been prescribed at least one of the classes of cardiovascular drugs of interest prior to the screening visit despite fully answering the questionnaire about medication at the screening visit. The analysis was performed with and without including aspirin as this is used for many non-cardiovascular indications. Even when aspirin was excluded 144 (32.9%) of the participants had been prescribed at least one

of the other classes of medication. For those with who failed screening and had pre-visit prescriptions the time to visit from last prescription is summarised in table 5.5 and the drugs classes prescribed to them are summarised in table 5.6. 36 people had a prescription within 6 months before the screening visit. When aspirin was excluded 33 people had a prescription in this time period.

Table 5.5: Time from last prescription of cardiovascular medication to screening visit for participants who failed screening who had previously been prescribed medication

	Time (days)	
	Including aspirin	Excluding aspirin
Minimum	1	1
1st quartile	197	222
Median	1428	1488
3rd Quartile	3820	3951
Maximum	8416	8416

Table 5.6: Drug classes prescribed prior to screening visit

Drug class	Frequency (number of people prescribed each class of medication)	
	High predicted CHD risk (n=146, 2.9% of those screened, 33.3% of screen fails)	Hypertension (n=291, 5.8% of those screened, 66.4% of screen fails)
Digoxin	1	1
Lipid regulating drugs	9	9
Thiazide and related diuretics	5	25
Loop diuretics	4	13
Potassium sparing diuretics	0	0
Potassium sparing diuretics with other diuretics	3	6
Diuretics with potassium	0	3
Beta-adrenoceptor blocking drugs	17	51
Centrally acting hypertensive drugs	0	1
Alpha-adrenoceptor blocking drugs	1	2
Angiotensin converting enzyme inhibitors	3	18
Angiotensin-II receptor antagonists	0	4
Nitrates	6	15
Calcium-channel blockers	8	19
Other anti-anginal drugs	1	0
Peripheral vasodilators	0	3
Oral anticoagulants	2	2
Antiplatelet drugs	7	12

1159 (26.2%) of the eligible population had been prescribed one of the classes of drug prior to the screening visit. The analysis was also done without including aspirin as this is used for many non-cardiovascular indications. When aspirin was excluded 1130 (25.6%) of the participants had been prescribed at least one of the other classes of medication. For those with pre-visit prescriptions the time to visit from last prescription is summarised in table 5.7 and the drugs classes prescribed to them are summarised in table 5.8. 167 had been prescribed medication within the 6 months before the screening visit (157 when aspirin was excluded).

Table 5.7: Time from last prescription of cardiovascular medication to screening visit for participants who were eligible for the study but who had previously been prescribed medication

	Time (days)	
	Including aspirin	Excluding aspirin
Minimum	1	1
1st quartile	723	744
Median	2407	2453
3rd Quartile	4596	4623
Maximum	8633	8633

Table 5.8: Drug classes prescribed to the eligible population prior to screening visit

Drug class	Frequency (number of people prescribed each class of medication)	
	BNP (n=2376)	MRI/BNP (n=2047)
Digoxin	2	10
Lipid regulating drugs	43	58
Thiazide and related diuretics	110	90
Loop diuretics	62	69
Potassium sparing diuretics	4	8
Potassium sparing diuretics with other diuretics	20	42
Diuretics with potassium	12	14
Beta-adrenoceptor blocking drugs	340	301
Centrally acting hypertensive drugs	2	1
Alpha-adrenoceptor blocking drugs	6	4
Angiotensin converting enzyme inhibitors	22	26
Angiotensin-II receptor antagonists	5	3
Nitrates	48	54
Calcium-channel blockers	75	58
Other anti-anginal drugs	0	3
Peripheral vasodilators	13	23
Oral anticoagulants	14	28
Antiplatelet drugs	59	80

Medication prescribed after screening visit

402 of those who failed screening had had no prescriptions of interest in the 6 months before screening and were therefore treated as not being on regular medication. Of these 171 participants had a drug prescription following screening (170 were prescribed prior to any CV event occurring and were therefore primary prevention and

1 was prescribed after a CV event so is likely to be for secondary prevention). Total follow up (until either first prescription, end of follow up or death) for this group was 1045 person-years. The first prescription rate was 164 (95% confidence interval 140-190) per 1000 person-years. The distribution of time to first prescription for these 171 participants is shown in table 5.9.

When aspirin was excluded from prescriptions either before or after screening 405 of those who failed screening had had no prescriptions of interest in the 6 months before screening and were therefore treated as not being on regular medication. Of these 172 participants had a drug prescription following screening (171 were prescribed prior to any CV event occurring and were therefore primary prevention and 1 was prescribed after a CV event so is likely to be for secondary prevention). Total follow up (until either first prescription, end of follow up or death) for this group was 1045 person-years. The first prescription rate was 164 (95% confidence interval 141-191) per 1000 person-years. The distribution of time to first prescription for these 171 participants is also shown in table 5.9.

Table 5.9: Time to first prescription of cardiovascular medication from time of screening visit for those who failed screening due to high cardiovascular risk, hypertension or dyslipidaemia and were prescribed medication after screening visit

	Time (days)	
	Including aspirin	Excluding aspirin
Minimum	0	0
1st quartile	62	59
Median	204	192
3rd Quartile	597	576
Maximum	2339	2339

4240 of those eligible to enter the study had had no prescriptions of interest in the 6 months before screening and were therefore treated as not being on regular medication. Of these 609 (14%) received at least one prescription between screening and the end of follow up. The total follow up (until either first prescription, end of follow up or death) for the eligible population was 16,424 person-years. The first prescription rate was 37 (95% confidence interval 34-40) per 1000 person-years. The distribution of time to first prescription for these 609 participants is shown in table 5.10.

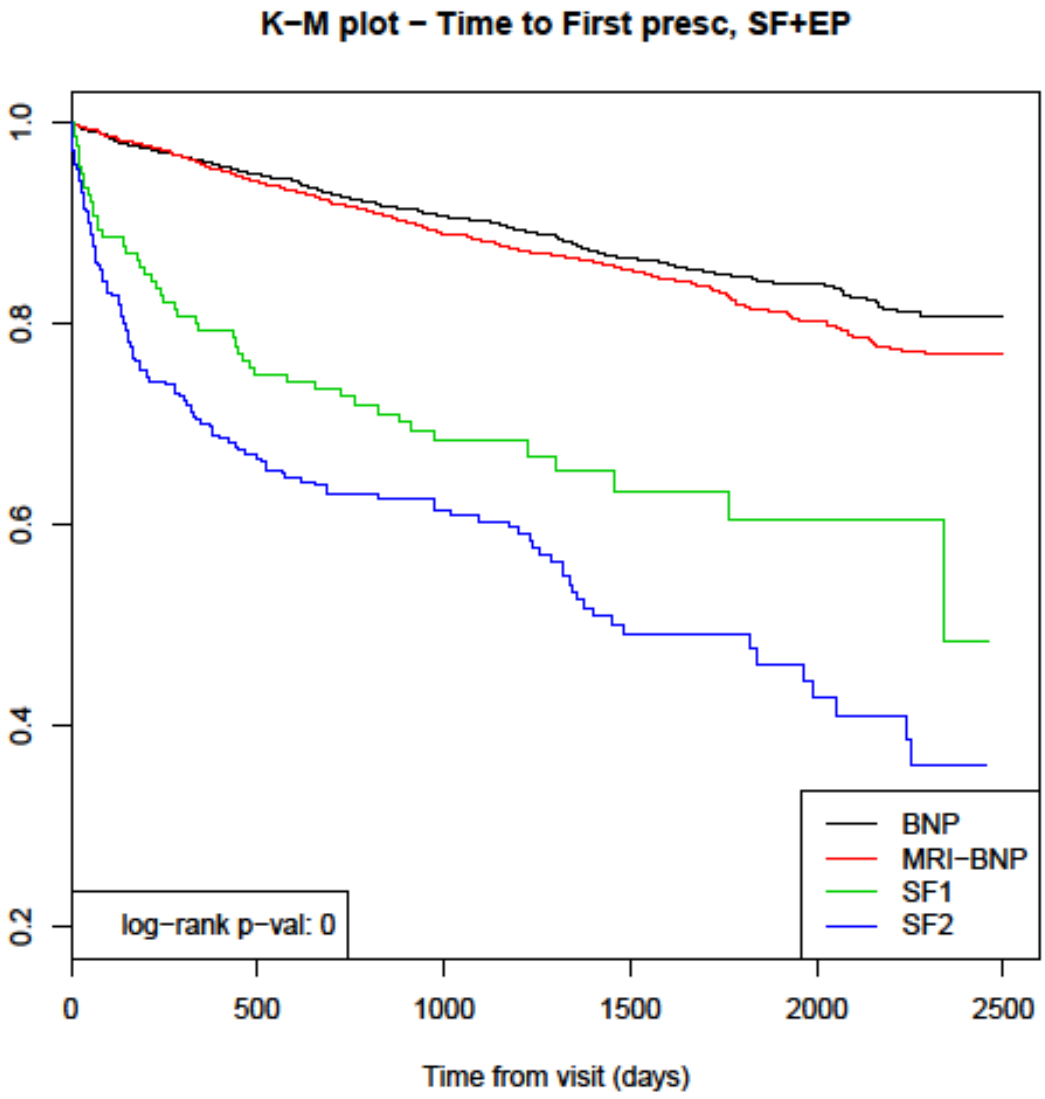
When aspirin was excluded from the analysis 4250 of those eligible to enter the study had had no prescriptions of interest in the 6 months before screening and were therefore treated as not being on regular medication. Of these 600 (14%) received at least one prescription between screening and the end of follow up. The total follow up (until either first prescription, end of follow up or death) for the eligible population was 16433 person-years. The first prescription rate was 36 (95% confidence interval 34-39) per 1000 person-years. The distribution of time to first prescription for these 600 participants is also shown in table 5.10.

Table 5.10: Time to first prescription of cardiovascular medication from time of recruitment for those who were eligible to enter the study and were prescribed medication after recruitment

	Time (days)	
	Including aspirin	Excluding aspirin
Minimum	1	1
1st quartile	321	320
Median	680	690
3rd Quartile	1217	1206
Maximum	2293	2293

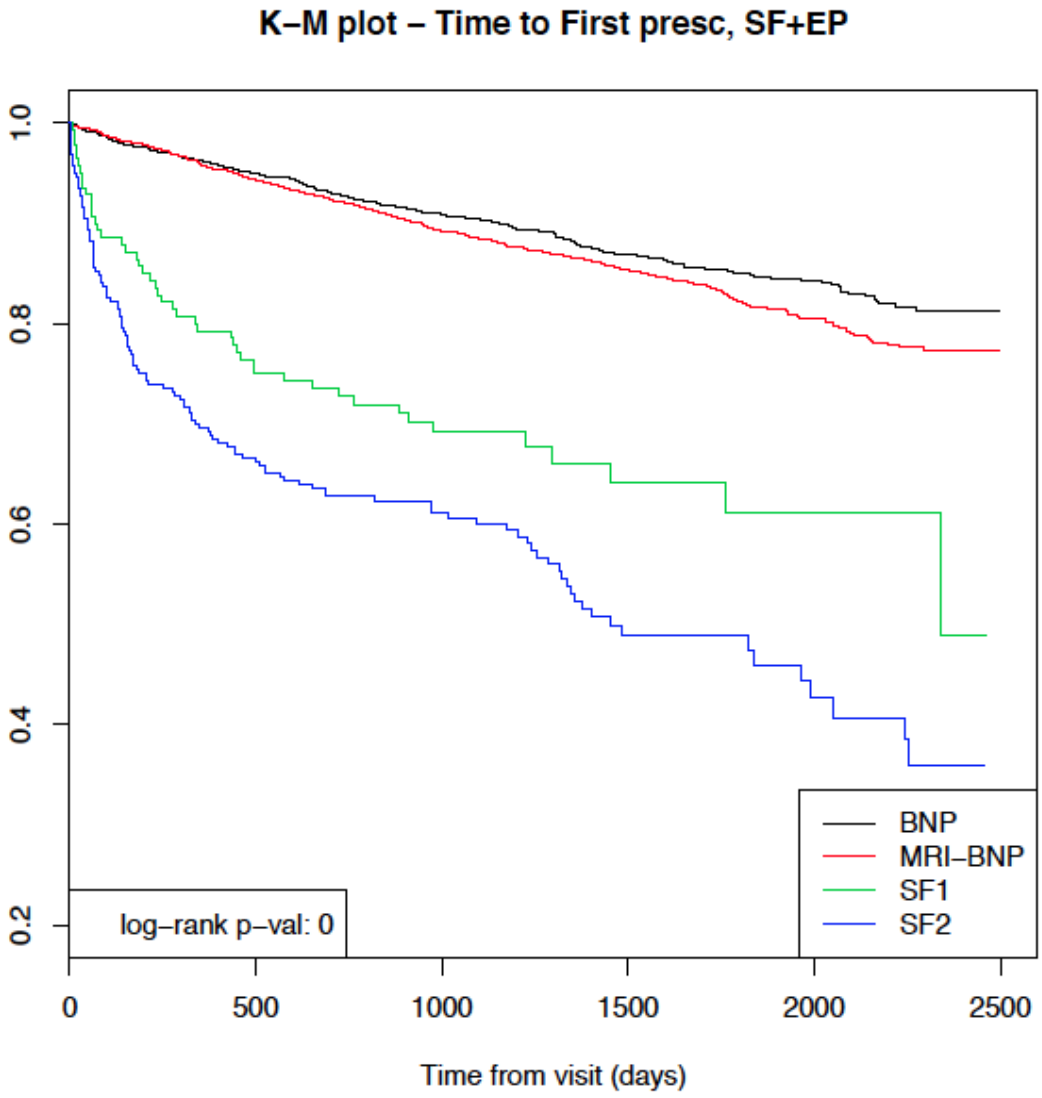
Figures 5.3 and 5.4 show time to prescription analysis (survival analysis) comparing those who failed due to hypertension and those who failed due to high CHD risk with the eligible BNP and MRI/BNP groups. Figure 5.3 includes aspirin and 5.4 excludes aspirin from the analysis. The classes of drugs prescribed to those who failed screening are summarised in table 5.11 and to the eligible population in figure 5.12.

Figure 5.3: Time to prescription analysis for those who failed screening due to high predicted CHD risk or hypertension and those eligible for the study (including aspirin)



SF1 is the group who failed screening due to high CHD risk score and SF2 is the group that failed screening due to hypertension.

Figure 5.4: Time to prescription analysis for those who failed screening due to high predicted CHD risk or hypertension and those eligible for the study (excluding aspirin)



SF1 is the group who failed screening due to high CHD risk score and SF2 is the group that failed screening due to hypertension.

Table 5.11: Drug classes prescribed after screening visit to those who failed screening

Drug class	Frequency (number of participants prescribed each class of medication)	
	High predicted CHD risk (n=146)	Hypertension (n=291)
Digoxin	0	1
Lipid regulating drugs	43	49
Thiazide and related diuretics	3	40
Loop diuretics	6	12
Potassium sparing diuretics	0	2
Potassium sparing diuretics with other diuretics	2	5
Diuretics with potassium	0	2
Beta-adrenoceptor blocking drugs	20	53
Centrally acting hypertensive drugs	0	1
Alpha-adrenoceptor blocking drugs	1	4
Angiotensin converting enzyme inhibitors	12	92
Angiotensin-II receptor antagonists	1	24
Nitrates	10	19
Calcium-channel blockers	17	61
Other anti-anginal drugs	1	1
Peripheral vasodilators	1	5
Oral anticoagulants	3	1
Antiplatelet drugs	14	20

CHD=coronary heart disease.

Table 5.12: Drug classes prescribed after screening visit to those who were eligible for the study

Drug class	Frequency (number of participants prescribed each class of medication)	
	BNP (n=2376)	MRI/BNP (n=2047)
Digoxin	1	9
Lipid regulating drugs	154	158
Thiazide and related diuretics	119	97
Loop diuretics	61	67
Potassium sparing diuretics	5	6
Potassium sparing diuretics with other diuretics	19	36
Diuretics with potassium	10	10
Beta-adrenoceptor blocking drugs	371	321
Centrally acting hypertensive drugs	4	2
Alpha-adrenoceptor blocking drugs	8	7
Angiotensin converting enzyme inhibitors	87	85
Angiotensin-II receptor antagonists	15	23
Nitrates	65	68
Calcium-channel blockers	104	99
Other anti-anginal drugs	1	6
Peripheral vasodilators	11	20
Oral anticoagulants	16	30
Antiplatelet drugs	89	125

Effect of medication prescription on CV event rate

1534 person years of follow up occurred for those who had failed screening due to high CHD risk, hypertension or dyslipidaemia and had not previously had a prescription for CV medication in the preceding 6 months. 24% of the follow up time occurred during exposure to one or more of the drugs of interest. A time updated Cox proportional hazards model including current exposure status, current age and sex showed no significant effect of exposure status on time to CV event (hazard ratio 2.8, 95% confidence interval 0.76-10.1, p=0.12).

When aspirin was excluded from the analysis 1545 person years of follow up occurred for those who had failed screening due to high CHD risk, hypertension or dyslipidaemia and had not previously had a prescription for CV medication in the preceding 6 months. 24% of the follow up time occurred during exposure to one or more of the drugs of interest. A time updated Cox proportional hazards model including current exposure status, current age and sex showed no significant effect of exposure status on time to CV event (hazard ratio 2.7, 95% confidence interval 0.75-10, p=0.13).

6. Discussion

6.1. Summary of main findings

The TASCFORCE study is a prospectively recruited observational study and was designed to assess the ability of a range of biomarkers (B-type natriuretic peptide, MRI derived left ventricular mass and stenosis burden detected by whole body contrast enhanced angiography) in addition to “traditional” risk factors to predict future cardiovascular disease in a low or intermediate risk group. The use of such research methodology for this aim is well established and forms the basis of the large epidemiological studies that have given us understanding of the aetiology of cardiovascular disease. Our use of this combination of biomarkers, using MRI and recruiting a population at low (<10% risk at 10 years) or intermediate (10-20% risk at 10 years) predicted risk of CVD at baseline makes this study unique. The intermediate and low risk groups are of particular interest as there is debate about how this group should be advised and treated in terms of primary prevention for cardiovascular risk. This study allows investigation of this difficult clinical group to help direct how they are managed.

We recruited 4423 individuals across Tayside to produce a cohort of volunteers free from cardiovascular disease and at low or intermediate predicted 10 year risk of cardiovascular disease. The study achieved its target recruitment by recruiting using a range of methods. The recruitment strategies ensured we recruited people from areas with different levels of social deprivation and from ethnic minorities to ensure it closely matched the local population. The recruitment involved screening over 5000 people so recruitment itself was a major success. All agreed to be re-contacted for future studies, for their data to be used over a number of years and for their data to be linked and followed up over time. We have established a large database of genotypic phenotypic and blood measures. It is one of the largest prospective studies of cardiovascular

disease using MRI globally. The well-characterised cohort and stored blood samples will also facilitate other observational studies of the development of cardiovascular diseases and novel biomarkers as events unfold in this Scottish population. Additionally it has provided opportunity to investigate associations of a wide range of baseline clinical, demographic, imaging and blood biomarker variables to help understand and generate hypotheses about the aetiology and development of CV disease. This represents a “Scottish Framingham” that will be a major resource for the study of cardiovascular disease for Scotland for years to come.

Originally it was intended that the study would be an intervention study investigating the effect of statins on those found to have evidence of subclinical disease however as the use of statins has become more widespread with an expanded evidence base the study was changed to an observational one.

The primary aim of the recruiting this cohort was to study the ability of a number of imaging and blood biomarkers to identify which individuals develop cardiovascular disease. Individuals with a left ventricular mass (both absolute and indexed for body size) and left ventricular mass/left ventricular end diastolic volume (a marker of concentric hypertrophy) in the upper quartile for their gender had a trend towards a higher rate of cardiovascular events and death compared to those in the lower quartile. However this did not reach statistical significance. This probably reflects the low number of events at this early stage in follow up and it is not possible to draw any firm conclusions about the ability of left ventricular parameters to predict CV disease until more follow up time has elapsed. Preplanned analyses at 5,10 and 20 years have been planned. There was also no significant difference in the rates of events between those with BNP levels above and below their gender median. There was a trend towards more cerebral (stroke) events in those with a higher BNP level and more coronary events in those with lower BNP levels. Again the low number of events so far makes it hard to draw any firm conclusions at this stage.

In addition to analysing the ability of the biomarkers to predict events the wealth of data collected allowed the analysis of normal values and associations of a wide variety of variables in a low and intermediate risk population. The main findings are summarised here and the reasons for the findings are discussed in more detail later.

At a preplanned review of BNP levels after the recruitment of about 1500 participants it became apparent that BNP levels in this healthy group were different between men and women. This resulted in gender specific medians having to be recalculated during recruitment and the recall of some participants for a scan. A number of studies published before the start of TASCFORCE had demonstrated a gender difference in BNP levels in healthy populations.[139-141] However as BNP levels in the healthy Tayside population were not known it was decided to determine these from the study population. In retrospect it may have been better to do a pilot study in a healthy population to determine normal BNP levels before the study started rather than have to retrospectively invite people for a scan. Increasing age, female sex, ex-smoking status, lower heart rate, lower total cholesterol and higher HDL were independently associated with higher BNP levels. The possible reasons for these associations are discussed in more detail later. Higher BNP levels were also associated with predicted CHD and CVD risk using ATPIII and ASSIGN algorithms respectively. This lends weight to the argument that BNP is a marker of vascular risk: as expected those with a higher predicted cardiovascular risk calculated using their risk factor profile have a higher BNP.

Left ventricular mass and left ventricular mass index was significantly higher in men than women reflecting their usually larger body habitus. Left ventricular end diastolic volume, end systolic volume, stroke volume and cardiac output were all significantly higher in men compared to women and ejection fraction was higher in women. However these differences remained when indexed for body size suggesting that

gender differences in cardiac size and function are not solely due to differences in body size but may reflect other differences such as metabolic rates, body shape (rather than size or surface area), physical activity, genetics and sex related anatomy. BNP was weakly correlated with end diastolic volume and stroke volume (both raw and indexed for body size) in men but not with any other left ventricular measures. The correlation with end diastolic volume may be expected as increased end diastolic volume may result in increased cardiac stretch which is known to stimulate BNP release. BNP was not correlated with any left ventricular measures in women. The weak or non-existent correlations with BNP may be because the vast majority of BNP levels were within a "normal" clinical range and because only those with a greater than median BNP were imaged thus reducing the range of BNP levels. Stronger correlations may have been seen if those with all BNP levels were imaged. Age was weakly, but significantly, inversely associated with LVM and LVMI (except when indexed by height$^{2.7}$) in men but only with LVM and LVM indexed by height in women. These associations persisted in a multivariable regression model suggesting that the association may be independent of other changes in CV risk that accompany age. Age was also associated with decreasing LV volumes, stroke volume and cardiac output in both men and women which persisted when corrected for other variables in the multiple regression models. These age related changes may reflect a combination of genuine myocardial atrophy with age (it is known that sarcopenia of systemic muscle is associated with age) and a biased population of older participants who are healthier and less likely to have LVH. Because age is a major determinant of cardiovascular risk older people may have a slightly more favourable risk factor profile of other factors to compensate for their age and result in a predicted score low enough to still allow eligibility. Systolic BP was positively associated with LVM and LVMI in both men and women as would be expected: a higher blood pressure increases cardiac work and can induce increase in cardiac muscle mass.

The vast majority of arterial segments in the angiograms were normal with no stenosis and of those that were abnormal most only had a mild stenosis which means we did recruit a truly low risk population in our study as planned. This is helpful as in future biomarker studies carried out when event rates are higher we will be able to hypothesise that with such a low atheroma score newly detected risk factors/biomarkers might be more likely to be considered aetiological rather than a secondary effect of atherosclerosis, which is a problem in secondary prevention studies which also aim to evaluate biomarkers. However the finding also demonstrates that a significant number of individuals at low predicted risk of CVD have evidence of possible disease. As follow up the significance, or otherwise, of this will become apparent. The standardised atheroma score was positively associated with predicted 10-year CHD risk in men and women. Age, systolic BP, ex-smoking status, heart rate, current smoking status and SIMD decile were independently associated with SAS. As above with LVM this suggests that the presence of subclinical stenosis is related to cardiovascular risk factors so is likely to reflect subclinical disease. The strongest association was with age suggesting this is the greatest driver of the association with predicted CHD risk. No other researchers have looked at this marker of subclinical disease in such a large population of people at low or intermediate risk of CVD and its prognostic capabilities are so far not reported. Follow up of the TASCFORCE cohort will allow us to investigate the relevance and implications of these findings.

6.2. Trial methodology

6.2.1. Recruitment

The study screened over 5000 individuals. Recruitment was assisted by study staff going to large employers and engaging at public events such as football matches and in supermarkets in addition to advertising and recruiting through primary care.

Additionally advertising through radio and regular press releases increased public awareness further. The multiple approaches to recruiting made it easier to reach a wider variety of people from different backgrounds ensuring we recruited a balanced population in terms of gender, race and social deprivation to reflect the local population. Actively going to people made it easier for members of the public to engage with the study as it required less active intent on their part. If recruitment had relied solely on recruitment through GP surgeries or hospitals it is likely that it would have been more difficult to reach so many people. A similar albeit less “one-to-one” method of approaching the population for screening has been adopted with success by programmes such as the Scottish bowel cancer screening programme which sends faecal occult blood sample cards in the post to men and women aged 50-74 years old.[238] However it has also been shown that people are more likely to participate in a screening programme if it is endorsed by the GP[239] so a mixed approach of approaching individuals, advertising and using primary care is likely to be best and helped recruit a large number of individuals. However despite recruiting a significant number of people the study did not quite reach its aim, based on the power calculation, of recruiting 5000 people at low or intermediate risk of cardiovascular disease because of the numbers found to have a CV risk score of ≥20% or hypertension (n=438) and these could not be replaced due to the booking requirements of the MRI scanner being allocated to other trials at the projected end of our study. The slightly smaller number of participants may result in the number of events at 5 year follow up is too small to draw any significant results. However the follow up in later years (e.g. at 10 years) is still likely to yield the required number of events to give sufficient power. The small under-target recruitment is therefore not likely to affect the eventual results but may just result in a longer time of follow up being needed to reach a significant number of events.

6.2.2. Ensuring representation of a cross section Scottish population

The study team aimed to recruit a population that represented as closely as possible the local population in Tayside. This would not only help assess the ability of a screening programme to enrol people from different ethnic and socioeconomic backgrounds but mean that any conclusions drawn by the study would be more likely to represent the population of Tayside as a whole and therefore be generalizable to this wider population. Therefore effort was made to recruit men, people from areas of social deprivation (using the Scottish Index of Multiple deprivation) and people from non-white-European ethnicity. These are groups that are recognised as being difficult to engage in screening programmes[240-244] and are often under-represented in studies.[245] They are also all groups that are recognised as being at increased risk of cardiovascular disease and therefore have potentially more to gain from screening and recruitment to clinical trials.

Despite aiming to recruit a representative sample men were still under-represented compared to women (1740 v. 2683, 39.3% v. 60.7%) compared to the Tayside population (48.4% v. 51.6%)[246] echoing the findings of other studies of screening programmes. The recruitment of participants from areas of social deprivation as indicated by Scottish Index of Multiple Deprivation (SIMD) was not markedly dissimilar to the local working age and total populations although those from areas of multiple deprivation were slightly under-represented (32% of the TASCFORCE population were below the median SIMD compared to 41% of the local population). Of those who were screened (i.e. before potential volunteers were excluded) only 41.2% were men suggesting even despite targeting recruitment at men they were still less likely to volunteer than women. Additionally the majority of those who failed screening due to high predicted cardiovascular risk or hypertension were men and more were from areas of multiple deprivation than the eligible population. Therefore the skewing of the population to women and those from areas with less deprivation is partly due to the screen failed population being skewed in the opposite direction. Therefore despite

targeting recruitment at these groups this may have needed to have been done more aggressively to account for the greater number of people from these groups who failed screening. The higher proportion of women may have an effect on the outcome data as men tend to have CV events at a younger age than women[247]: the over-representation of women may therefore mean that events take longer to accrue than has been predicted. The slight under-representation of those from areas of social deprivation may have a similar effect. It is known that living in areas of social deprivation is associated with a lower life expectancy and healthy life expectancy.[248] Except for those recruited as part of the South Asian substudy we did not collect ethnicity data on all participants. Therefore it is not possible to determine if the ethnic make up of the study population reflects the local population. However Asian and other ethnic groups are only a small percentage of the local Tayside population. 96.8% of the Tayside population is white with 2.1% of Asian origin and 1.1% from other ethnic groups.[246]

The reasons for underrepresentation of certain hard to reach groups has been investigated previously; fear of screening programmes (particularly of finding abnormality or disease), past negative experiences with healthcare, lack of motivation and dissuasion by peers have been shown to influence uptake.[249, 250] The social and demographic environment has an influence on screening engagement beyond individual characteristics such as gender and ethnicity.[251] A large qualitative study into engagement with cancer screening found that those with a lower socioeconomic status rated the benefits of screening lower, and had more fear and a more fatalistic attitude to cancer.[252] Therefore it is likely that attitudes and beliefs in hard to reach groups may need to be better understood and addressed to improve uptake further rather than just targeting existing screening programmes at these groups. However we have shown that this targeted approach is still worthwhile. This is particularly important as those from areas of deprivation and men are at increased risk of CV disease so are more likely to benefit from intervention.

Those from areas of social deprivation and ethnic minorities are also under-represented in clinical trials.[245] The reasons for under-representation in socially deprived groups is not fully understood and motivation for participation in clinical trials remains elusive however there is likely to be some overlap of the reasons for poor engagement in screening programmes described above. Different people are likely to volunteer for different reasons and this may depend on the aims of each individual study: some will volunteer purely for altruistic purposes whereas at the other end of the spectrum others will only volunteer if they personally see some benefit. This will be influenced by what the study involves. This personal gain motivation may be reflected in the number of people who enrolled in TASCFORCE but did not consent or attend for their MRI scan: the ability to get a health check and blood test including lipid profile may have been seen as advantageous to that individual at relatively little personal cost whereas attending for an MRI scan may not have been perceived as bringing any personal benefit. Financial incentives to participate in trials have been investigated and were found not to increase recruitment of those from lower socioeconomic backgrounds.[253] We believed that access was also important and thus actively sought out this population in areas near to their locale, and at venues most people attend (for example football grounds, supermarkets and workplaces).

An area that has been covered more in the literature is that of reasons for underrepresentation of ethnic minorities in research. TASCFORCE specifically recruited participants of South Asian ethnicity as part of the South Asian sub-study. They were matched with white European participants to facilitate comparison of baseline parameters and CV outcomes between the two ethnic groups and therefore better understand the differences between them. 38 (0.9%) of the total recruited population was of South Asian origin compared with 2.1% of the local population being from Asian origin.[246] However the ethnicity of the rest of the study population was not fully determined and documented thus preventing accurate description of the

population in terms of ethnicity. No black participants were recruited and although some of East Asian origin were they accounted for less than 1% of participants, which is very close to the local population proportion. This lack of characterisation is common particularly in the UK although it may be marginally better in the USA.[254] A review of recruitment of ethnic minority groups describes some of the barriers to recruiting representative populations in trials.[245] Although TASCFORCE did not explicitly exclude participants from ethnic minorities it is possible that their involvement could be indirectly hindered. For example for some English may not be their first language which could provide barriers to understanding recruitment material, participant information sheets and the consent process. Because of the extra work (and therefore cost) involved many studies do not routinely translate study materials into different languages or provide interpreters. Cultural beliefs (for example modesty and reluctance to be examined by study staff) may also inhibit some from participating. Additionally the concept of clinical trials is a “Westernised” one so it has been suggested that it may not yet be part of the “cultural repertoire” of ethnic minority communities. Therefore extra effort may need to be made to make trial participation more appealing and easier for ethnic minorities. Additionally more effort should be made to describe the ethnic make-up of study populations such as the TASCFORCE cohort so that it can be determined if findings can be extrapolated to other populations.

6.2.3. Screening method

The screening process for recruitment to TASCFORCE involved the comprehensive collection of a range of “traditional” risk factor and demographic data. This has enabled the study population to be well characterised and described, has facilitated the analysis of associations of these data with the blood and imaging biomarkers and formed the basis of the CV risk estimation. It also allowed targeted advice to be given to participants to improve modifiable risk factors through lifestyle and diet modification.

The use of leaflets produced by the British Heart Foundation re-enforced the verbal information given.

Where the initial BP reading was elevated (>145/90mmHg) and would have therefore led to exclusion of the participant up to a further two readings were taken. If more than one measurement was taken the lowest of the readings was used in analysis which is in keeping with current guidelines from the British Hypertension Society (BHS).[10] The use of a cut-off of 145/90mmHg is slightly higher than that which diagnoses stage 1 hypertension and according to the BHS guidelines should lead to an assessment for end organ damage and overall assessment of cardiovascular risk. Participants found to have such a blood pressure were referred to their GP for further assessment and management. The screening process therefore identified a significant number of people who had hypertension who were unaware of their diagnosis potentially allowing treatment and full assessment earlier than would have been the case if they had not participated. This shows that despite the quality outcomes framework (QOF) driving the checking of blood pressure by GPs a significant number of people had undiagnosed hypertension. This may reflect the reluctance of some fit and healthy people to attend their GP for screening. The sole use of one-off BP readings may have led to the exclusion of some individuals with white coat hypertension who may have been eligible if they had undergone ambulatory or home blood pressure monitoring as advised by the BHS guidelines. However this would not have been practically possible within the resources available for the trial so follow up was left to the discretion of the participants' GPs.

All those recruited had their predicted 10-year coronary heart disease risk calculated using the algorithm in the bedside cholesterol analyser. This used the ATPIII algorithm based on the Framingham cohort.[229] Around the time of design and start of recruitment for TASCFORCE the ASSIGN score was developed[41] and is now recommended for use in Scotland[5] to estimate people's cardiovascular risk. The use

of ATPIII in TASCFORCE has resulted in a difference between the method used for risk estimation in the study and in clinical practice. The two scoring methods have some significant differences and are therefore not interchangeable. ATPIII predicts coronary heart disease whereas ASSIGN also includes prediction of non-coronary cardiovascular disease particularly stroke. SIGN, ECS and AHA guidelines now all recommend that risk estimation includes this broader range of CV disease. The two scores were strongly correlated but the ASSIGN score on average was higher than the ATPIII score. This would be expected due to the broader outcomes predicted by the ASSIGN score. ASSIGN also includes additional variables (family history of CV disease, measure of social deprivation and history of rheumatoid arthritis) and treats variables as continuous rather than grouping them in brackets. The ASSIGN score was derived from a Scottish study population more similar to our study population whereas the ATPIII score was derived from a study population in the United States. As may be expected the different methods and meaning of their results led to the reclassification of some individuals in terms of their risk category and we demonstrated differences between individuals' ATPIII and ASSIGN derived scores. More people were "up-classified" to a higher risk group using the ASSIGN score than were "down-classified" and on average ASSIGN scores were greater than ATPIII scores. This suggests that if the ASSIGN score had been used in the study a significant number of those recruited (258) would have failed screening and should be considered for starting on cholesterol lowering medication and 52 of those who failed screening due to high predicted CV risk would actually have been eligible for the study. This means that more people were recruited than may have been possible if the ASSIGN score had been used to assess eligibility. Additionally those recruited may have a higher rate of events than would otherwise be predicted. This could result in a higher than expected number of events as follow up continues. It will also allow us to determine in 10 years time which scoring method is most accurate in this population.

Random blood glucose measurement was introduced approximately halfway through recruitment for the study. It had been excluded due to the difficulty of asking volunteers to fast as previous normal volunteer studies had shown potential recruits were put off by a fast. However we decided to measure random samples in the latter half of the population giving us sufficient data to investigate links in later data linkages. As this was not measured for all participants an elevated level was not used to exclude people from the study - it is not possible to ascertain that those who did not have a level checked did not have diabetes. Additionally even if the random blood glucose level was >11mmol/l this would not be sufficient to diagnose diabetes in the absence of symptoms without a second confirmatory plasma determination[255] making diagnosis of diabetes at a one off visit impossible. Therefore if the level was >7mmol/l participants were informed of the result and asked to have a fasting sample rechecked at their GP to determine if they had diabetes. Glucose measurement was therefore used more to flag up the need for further investigation rather than an exclusion criteria. Currently stored samples are being used to check blood glucose levels for those who did not originally have a level checked, which will allow a more robust usage of the data, but these data are not yet available for analysis in this thesis.

In addition to the opportunistic education about modifiable cardiovascular risk factors offered to all those who were screened all individuals who were found to be at high risk of cardiovascular disease or were hypertensive were referred to their GP for further assessment and consideration of treatment. The use of such a proactive screening programme therefore helped identify a large number of people at increased risk of cardiovascular disease who may not otherwise have had this risk recognised. This potentially has allowed monitoring and/or interventions to be put in place to reduce the incidence of CVD. Prescription of cardiovascular medication following screening is discussed later in section 6.3.1. The opportunistic education may in fact have an effect and lower the event rate as follow up continues but it was not considered ethical to do otherwise.

Those who failed screening due to high predicted CHD risk were older, mostly men (97%), mostly smokers (58%), had a slightly higher blood pressure, total cholesterol, lower LDL and higher HDL showing the increased risk is due to a combination of risk factors. The fact that almost all were men shows the power of male gender on cardiovascular risk. This contributed to the eligible population containing fewer men as discussed earlier in section 6.2.2. Despite the CHD score not directly using SIMD data more of those excluded due to high CV risk were from areas of multiple deprivation (33.5% of those who failed due to high predicted risk compared to 24.3% of the eligible population were from SIMD deciles 1-4). This shows that traditional cardiovascular risk factors are associated with social deprivation although this has also been shown to be an independent factor hence it's inclusion in the ASSIGN score as discussed earlier.[41] Those who failed screening due to hypertension were older than the eligible population probably reflecting the association of increasing BP with increasing age. This will again have resulted in the exclusion of older people and contributed to an eligible population that is skewed towards younger participants.

As only those with a cardiovascular risk of less than 20% in 10 years were recruited into the main study those imaged and with BNP levels are likely to have a narrower range of BNP levels and less variation in MRI findings than if a more diverse population was studied in more detail. However this low/intermediate risk group were those of most interest as there is uncertainty as to how best treat them so the limited resources for the study were targeted at this group. It is recognised however that this may have limited the ability of the study to find significant differences in imaging and biomarker parameters. With more financial resource it would have been preferable to investigate a wider range of participants.

We used BNP to determine who should be offered an MRI scan. As described in detail in the literature search there is a large body of evidence showing that natriuretic

peptides are associated with impaired vascular function, calcification and presence of subclinical disease and importantly is able to detect individuals with subclinical cardiovascular disease. Levels are also associated with increased estimated and actual cardiovascular risk in a variety of populations. BNP measurements from different assays may not be interchangeable[139] so median values and distribution obtained in TASCFORCE cannot routinely be used in other populations unless the same assay is used. Assays for both BNP and NT-proBNP are available. NT-proBNP has a longer half life and is more stable over a period of time so may have been a better test to use. However at the time of the study initiation the BNP assay was cheaper and the aim was to screen a large number of people. Therefore a pragmatic decision was made to use BNP rather than NT-proBNP.

Interestingly, if puzzling, using data linkage through the Health Informatics Centre in Tayside, it has subsequently been found that a proportion of people who were deemed eligible to enter the study based on their negative history for CVD or high risk, had apparently previously been prescribed cardiovascular medication. This comprised lipid regulating medication, antihypertensives, antiplatelets and antianginals. Many had not received a prescription for a considerable amount of time (median time from last prescription was 2407 days) however some (167, 3.8%) had been prescribed medication in the 6 months prior to being enrolled in the study and at least one participant had received a cardiovascular medication the day before recruitment. This may suggest that either these people were not taking medication they had been prescribed, did not declare they were taking them at time of recruitment or that there are errors in the linkage programme and we are following up on all of these to ascertain which is the case. Alternatively they may have received the medication for indications other than for cardiovascular disease. For example aspirin may have been prescribed as an analgesic (e.g. for migraine), anticoagulants for venous thromboembolic disease, calcium channel blockers for cluster headache or Raynauds prevention or beta blockers for essential tremor. However even when analysis was

done excluding aspirin 1130 (25.6%) of the eligible population had been prescribed cardiovascular medication compared to 1159 (26.2%) when aspirin was included. The difference between the two analyses is not large suggesting the issue of medications being used for other purposes may not be that great a problem. Further analysis is ongoing looking at whether prescriptions were acute or repeat prescriptions and what the indications may be using the GP coding data. However this illustrates one of the difficulties of interpreting linked follow up data without direct access to clinical notes.

6.2.4. Imaging method

As MRI scanners become more widely available and scanning techniques have been refined it is becoming increasingly feasible to use them to screen for cardiovascular disease. The lack of ionising radiation also makes the modality more acceptable for use in mass screening compared to other modalities which have an evidence base for detecting subclinical disease such as CT for calculating coronary artery calcium scores. The MRI used in in TASCFORCE also images a wide range of parameters (both arterial and cardiac) thus potentially increases the sensitivity for detecting abnormality compared to more targeted imaging such as coronary artery calcium scores or carotid intima media thickness measurement. Therefore MRI was chosen for this screening study. The TASCFORCE study is unique in combining cardiac and whole body angiography in a large cohort of truly low risk people. The technique has been refined by the study team and uses what would otherwise be “deadtime” in the scan protocol to gain further images. In this way comprehensive imaging of the heart and arterial tree is possible in an acceptable scan time. Other studies have used individual components of the imaging protocol but have either not combined it with whole body angiography or have imaged people with a variety of baseline cardiovascular risk profiles. For example the MESA study[174] has used MRI cardiac imaging but not whole body angiography in individuals free from CVD and the Dallas Heart study[175] included a thoracic MRI scan but did not specifically exclude those at

high risk of cardiovascular disease and again did not include MRI angiography. Those who have used contrast enhanced MRI angiography to quantify whole body atheroma burden (some along with cardiac imaging have used populations who are either much smaller, diabetic, older, had pre-existing or suspected CV disease and/or had mixed background cardiovascular risk (i.e. those at increased risk were not excluded)[207-209] Therefore the TASCFORCE population and its imaging data is unique and permits characterisation and determination of normal values and correlations between the variables for this a normal low risk group. The coronary arteries were not imaged in this study. This would have entailed a longer imaging time which would have impacted on participant acceptability and had an implication for resource utilisation. Atherosclerosis is a systemic disease and atheroma in peripheral arteries has been associated with coronary artery disease (209). Therefore the pragmatic decision was made to image the wider arterial tree and look for a wider range of cardiovascular abnormalities whilst limiting the scan time to a reasonable one. There is also local expertise in performing and interpreting cardiac MRI and whole body MRA.

25.5% of those eligible for a scan did not complete a scan which may limit the imaging technique's acceptability as a screening tool. 4.0% were due to claustrophobia but significantly 18.9% either did not consent for an MRI scan or did not attend for their appointment. This compares to a 16.3% "did not attend" rate for colonoscopy in the UK bowel screening programme[238] so is not dissimilar. It is possible that potential recruits were keen to get their blood pressure and cholesterol checked (if this was at their place of work it will have taken very little of their time) but were not prepared to attend for the scan. As they were identified as not being at increased risk of CV disease individuals' perception of the need for or value of an MRI scan may have been reduced. Interestingly those who declined or were unable to have an MRI scan had a small but statistically significantly higher resting heart rate which may reflect a degree of anxiety in those who declined a scan. They also had a marginally higher systolic blood pressure, which may support this theory. This may have produced a skewed

population of people who completed a scan who were potentially “healthy responders” or “worried well”. It would be interesting to have explored the views of those who did not attend for or declined an MRI scan to understand factors influencing the decision to attend. This would allow factors that prevent or dissuade people undergoing scanning to be tackled in a potential future screening programme.

The cardiac imaging protocol is similar to other groups who have used cardiac MRI to image healthy populations using a steady state free precision (SSFP) sequence. However TASCFORCE used a 3.0T scanner whereas all the other the other groups have used 1.5T scanners[177, 256-258] making TASCFORCE the only study to use 3T SSFP cardiac imaging in a healthy population. The TASCFORCE population is also much larger (1515) than any of the other three studies who studied 1140 people between[177, 259] them with the most in one study being 852.[258] Other groups have studied cardiac volumes and mass in larger populations using MRI but have used turbo gradient echo (TGE) sequences.[182, 183, 260-262] Such protocols have been shown to give different values for mass and volume compared to SSFP[256] which is thought to be due to improved delineation of the endocardial border because of better definition with SSFP. Therefore values from the 2 protocols are not interchangeable. Other larger cardiac imaging studies have also studied populations of mixed cardiovascular risk.

As with other groups ECG gated breath-hold images were acquired. There is some variation between studies in the thickness of slices. TASCFORCE acquired 6mm slices with a 4mm gap whereas others using SSFP have used slices of 7mm with gaps ranging from 0 to 4mm. The method we used for determining cardiac volumes and masses is similar to those used by other groups. We used manual placing of epicardial and endocardial contours as did all the groups using SSFP MRI protocols. One difference between studies is the inclusion or exclusion of papillary muscles in the left ventricular mass. In TASCFORCE papillary muscles were excluded from the left ventricular muscles mass and were ascribed to the blood pool unless they were

indistinguishable from the myocardial wall whereas all but one[177] of the other SSFP studies included them in the left ventricular mass.[259] For groups using TGE protocols there has been some variability in inclusion of papillary muscles as there appears to be lack of agreement about the best method. The MESA group excluded papillary muscles from the LV mass as they found it resulted in greater reproducibility[191] as did the Framingham Offspring study[183] whereas the Dallas Heart Study group[262] included them in the left ventricular mass.

TASCFORCE used a specific gravity for myocardium of 1.05g/ml identical to that used by the Dallas Heart study group and Lorenz *et al* whereas the MESA study group used a slightly different specific gravity of 1.04g/ml which could account for other differences (albeit small) in calculations of left ventricular mass.

The differences in methodology both for image acquisition and analysis need to be considered when comparing findings between groups. Calculation of LV volumes and mass is well used by the different groups and is similar to the methodology in TASCFORCE however the different acquisition protocols, slice and gap sizes and attribution of papillary muscles could potentially introduce different levels of calculation error.

Left ventricular mass and other variables are commonly indexed to account for body size. Scaling of cardiovascular parameters is rarely performed in clinical practice whereas it is routine in paediatric medicine despite adults having a wide range of body sizes. Therefore it seems justified to account for this natural variation in body size. Various different methods of indexing left ventricular mass to correct for body mass, size and height have been described and used by different research groups. We have used a variety of methods (dividing by height, $height^{1.7}$, $height^{2.7}$, body surface area (using 2 different calculations for estimating body surface area)). This will allow us to see which method of indexation may best predict future cardiovascular disease.

A review of different methods of indexing cardiovascular parameters explains in detail the strengths and limitations of various methods of indexing.[263] The authors argue that ratiometric scaling methods (simply dividing a left ventricular parameter by a measure of body size) are problematic as they rely on the relationship between the two being linear and that dividing a 3 dimensional LV measure by a 2 dimensional body size measure (eg BSA) is theoretically flawed. They support this theoretical shortcoming with evidence from studies. They give evidence that allometric scaling (LV measure/body size measure^{x}) is superior at indicating the normality of cardiovascular function and size for a given patient size. For this reason the use of allometrically derived indexing (for example use of height$^{1.7}$ and height$^{2.7}$) may be preferable to the other ratiometric indexes.

It is also important to consider which measure of body size is best to use. Obesity and therefore body surface area are associated with CV disease. However height and CV are also associated.[264] For the purpose of predicting CV disease indexing for height may seem reasonable as this is a non-modifiable factor. Those who are taller are also likely to have larger hearts. However correcting for body surface area which increases with body mass or BMI may not necessarily be desirable if the results are to be used for this purpose. Increased body mass (and therefore body surface area) is associated with increased risk of cardiovascular disease so correcting for this may remove or attenuate an important prognostic indicator. The review of indexing[263] supports this view. Body surface area does not take account of how much mass is metabolically active tissue (which the heart's aim is to supply with nutrients and oxygen). For example an athlete will have more tissue with greater metabolic potential than a non-athletic obese person despite potentially having the same BMI. Body surface area and body mass index do not account for these important morphological differences. The validity of the Dubois calculation is also questionable as this was derived from a study of only 9 cadavers about 100 years ago.[235] The allometric associations between fat

free mass and LV structure and function are better than using BSA or total body mass[263] however as fat free mass determination is difficult the use of height (as we have used as one indexing method) is a reasonable alternative. In TASCFORCE indexing by height$^{2.7}$ reduced correlation with height and weight more than indexing by height$^{1.7}$ or height. When we indexed by BSA correlation of LVMI with weight reduced further but not with height. The lack of complete removal of correlation with height and/or weight led the MESA group to index by dividing actual LV mass and volumes by predicted LV mass and volumes respectively calculated using an allometric regression model of non-obese, normotensive sub-population to predict LV mass based on height, weight and sex.[191] The Dallas Heart study group have indexed LV mass by fat free mass (albeit ratiometrically) as well as for BSA and height$^{2.7}$ to account for body compensation.[184, 262] The Framingham heart Study Offspring study have indexed left ventricular measurements for height, height1.7, height 2.7, BSA and fat-free mass.[177]

We also calculated LV mass/LV end diastolic volume (LVM/LVEDV) as a marker of concentric remodelling. In concentric remodelling the left ventricular mass increases to a greater degree than the left ventricular volume so this ratio increases. Concentric remodelling has been associated with decreased systolic function.[265] Importantly LV mass/volume ratio has been positively associated with incident coronary heart disease and stroke[181, 191] showing the potential importance of this measure in predicting disease.

The protocol for whole body angiography was developed locally on a subset of the TASCFORCE participants to optimise the contrast dose and delivery rate to maximise image quality.[203] The reduction in total contrast dose and the use of an asymmetric bolus regime (10ml and 15ml) reduced the level of venous contamination during the second bolus injection. The term “whole body” MRI angiography is commonly used although as in the case of TASCFORCE does not usually image every artery but just

the aorta and main branches. For example we did not image coronary arteries. This would require ECG gating and is therefore technically much more difficult.

A locally developed scoring system for whole body angiography was used in TASCFORCE. This assessed the presence of luminal stenosis in a range of arterial segments ranging from the carotid arteries to the leg vessels. Increasing scores are given for increasing degrees of stenosis and the score is then standardised and takes account of segments that cannot be scored due to technical problems with the imaging or lack of tolerability of the scan meaning not all segments were imaged. This gives a standardised atheroma score that reflects the whole-body burden of stenosis. As well as being used by the same research team locally in different study populations similar scoring systems have been devised by other research groups. Various atheroma scoring systems are in use by different research groups. The systems in use are subtly different in both the way that degrees of stenosis are scored and how these are combined to give a total body atheroma burden. They have also been performed in different populations of patients. For comparison the scoring systems used by different groups are summarised in table 6.1.

Table 6.1: Whole body atheroma scores reported in the literature

Study group/lead author	**Patient group**	**Vessel scoring system**	**Method of combing scores**
TASCFORCE	Over 40s free from CV disease and with predicted risk <20% over 10 years	31 arterial segments 0=no stenosis or wall irregularity 1=<50% stenosis 2=50-69% stenosis 3=70-99% stenosis 4=occlusion Point added for aneurysm	Standardised atheroma score (SAS) derived by summing segment scores, dividing by number of interpretable segments divided by 4 (maximum score for segment) multiplied by 100.
PIVUS[208]	70 year olds with mixed vascular risk profile	26 arterial segments 0=no stenosis or wall irregularity 1=<50% stenosis 2=50-99% stenosis or occlusion	Segments summed in 5 territories (carotids, aorta, renal arteries, pelvic/upper leg, lower leg) divided by maximum possible score in that territory multiplied by 100. 5 territory scores summed to give a total atheroma score (TAS).
Findiesen[207]	Patients with diabetes	22 arterial segments 1=normal or mild wall irregularity 2=no significant stenosis 3=single stenosis>50% 4=multisegmental stenosis >50% 5=fading vessel 6=occlusion	Mean of segment scores.
Lehrke[209]	Patients suspected of having coronary artery disease	40 arterial segments 1=normal 2=<25% stenosis 3=26-50% stenosis 4=51-75% stenosis 5=76-99% stenosis 6=occlusion	Segment scores summed and divided by number of analysable segments to give atherosclerosis score index.
Ruehm[205]	Patients with peripheral arterial disease	15 arterial segments (only from aorta and inferiorly) 0=normal 1=irregularity and <10% stenosis 2=<50% stenosis 3=≥50% stenosis 4=occlusion	Not combined into a total score.

The scoring systems in use differ in 2 key ways: the cut off between different degrees of stenosis and how the segment scores are combined to give a total score. The first of these differences means that some give more weight to lesser degrees of stenosis or wall irregularity than others. Therefore those using lower cut-offs would be expected to give higher total scores for lots of subclinical disease. The cut offs used may depend on what the score is being used for. If being used to screen for early stage disease (as with TASCFORCE) building in the sensitivity to detect early changes is important and distinction between more severe stenosis may be less important (for example between our scores 2, 3 and 4). It is significant that we included wall irregularity in the "<50% stenosis" group to detect very early stage disease; not all groups have done this. For screening for early disease the total number of vessels affected may be more important than the degree of stenosis found.

The second difference means that different arterial territories may be given greater weighting than others. For example the system used in the PIVUS group results in segments in territories that have less segments (such as the aorta and renal arteries, 2 segments each) contribute more to the overall total atheroma score than segments in territories with more segments (such as the pelvic/lower limb with 10 segments). TASCFORCE like most of the other scores have given equal weight to each arterial segment in the total body score. Weighting may be appropriate if it was shown that some segments are more important prognostically than others however this is not yet clear in this asymptomatic group. The data is still available at individual segment level to allow future analysis of different weightings to produce total scores and the impact this may have on predicting cardiovascular events. Ongoing follow up in TASCFORCE will allow this to be investigated.

One limitation is due to the different width and length of the segments. By measuring stenosis in terms of percentage luminal narrowing larger arteries such as the aorta require a much greater thickness of plaque to produce a greater than 50% stenosis

than a narrower distal leg artery. The aorta could therefore have quite extensive atheromatous disease which may have serious clinical implications but still have a less than 50% narrowing and therefore score lowly. Conversely a small atheromatous plaque in a narrow distal artery will cause a potentially greater percentage narrowing and therefore score much higher. The length of arteries will also have an effect. Some segments are short (for example the innominate artery) and so have a theoretically smaller chance of having a stenosis compared to a much longer arterial segment. This may explain why the rate of abnormality detected in the innominate artery was so low. However it still contributes the same to the overall score as longer arteries. This may not be as important when the method is being used to detect subclinical disease as the presence of rather than the degree of atheromatous may be more important.

The use of “luminography” rather than looking at wall thickness could be criticised as not theoretically detecting atherosclerosis. However as discussed later, the correlation with predicted cardiovascular risk that we have demonstrated lends support to its suitability to detect subclinical disease.

All the arterial segments in the MRAs were assessed for the presence of aneurysms. Aneurysms and atherosclerosis have overlapping risk factors and some commonality in their pathology and aetiology so it is conceivable that they could represent an increased risk of cardiovascular disease. The presence and increasing diameter of abdominal aortic aneurysm is associated with increased risk of non-aneurysm related mortality and cardiovascular mortality suggesting it may be a marker of cardiovascular risk.[266] However it is less clear how significant the presence of aneurysm is for predicting cardiovascular risk or what the significance of aneurysms in other arteries is. None of the other groups using scoring systems for WB CE-MRA have included aneurysms in their whole body score. Currently in our score the presence of aneurysm adds one to a score for the segment affected so contributes the same as minor luminal narrowing and significantly less than the presence of significant stenosis. The presence

of aneurysms affected only 40 out of 46601 (0.09%) total segments analysed whereas atheroma affected 2133 (4.6%) of segments affected so contributed significantly more to standardised atheroma scores.

Initially the coeliac trunk was assessed for stenosis however standardised atheroma scores have been calculated both including and excluding this segment because of concerns about significant artefact in this segment. This illustrated by the disproportionately high level of recorded stenosis in this artery compared to other segments. This phenomenon on MRI had been described previously where stenosis appeared significantly more prevalent on MRI images obtained at end expiration compared to inspiration.[267] It is likely this artefact is due to compression of the coeliac artery by the median arcuate ligament which is a well-recognised anatomical variant. For this reason it is not clear whether the stenoses we observed in the segment are genuine. It is notable that the majority of those using scoring systems have not included the coeliac artery in their analyses.

We demonstrated almost perfect inter-observer agreement (Fleiss kappa values>0.80) in all the arterial segments except the coeliac artery demonstrating that the technique is reproducible. The reduced (but still substantial) agreement for the coeliac trunk is most likely to reflect the difficulties in interpretation due to artefact outlined above.

6.2.5. Strengths and limitations

Strengths

We have recruited a large cohort of people from a variety of socioeconomic backgrounds. Our gender split is similar for the population of Tayside despite a non-significant slight female bias. We ensured at least a 0.9% ethnic minority population in a population where this is at 2.8%.[246] Comprehensive collection of baseline clinical and demographic variables has allowed the cohort to be well characterised and will permit investigation of associations of baseline variables with each other and future

events and disease. It also assists characterisation and investigation of a large Scottish population. This will help generate hypotheses about possible aetiology of cardiovascular disease and cardiovascular risk. Other cardiovascular cohort studies such as Framingham have sampled or studied populations with different ethnic mixes or in different cultural, political and healthcare backgrounds from where findings may not be directly transferable to the Scottish populations.

The imaging and blood biomarkers being investigated have an evidence base showing association with clinically relevant outcomes. Rather than using entirely new techniques and or markers TASCFORCE is building on this evidence to investigate whether incremental value is added using the unique combination of biomarkers. However blood from each participant has been stored and will be available for analysis of emerging or new biomarkers in the future allowing the study to remain contemporary as the research in the field develops as the study follow up progresses. Additionally DNA has been stored and can be duplicated using polymerase chain reaction to investigate genetic determinants of cardiovascular disease.

TASCFORCE is assessing the ability of a screening programme incorporating MRI derived left ventricular mass and BNP to predict future cardiovascular events thus potentially allowing targeted intervention to be improved. The UK National Screening Committee has produced criteria for appraising screening programmes (see below in table 6.2).[268] The programme being investigated in TASCFORCE either fulfils or is seeking to answer a number of these criteria and therefore the method is a potential viable screening technique.

Table 6.2: Criteria for screening programme and how TASCFORCE fits these

Criteria	TASCFORCE
The condition should be an important health problem.	CV is a leading cause of death.
The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.	Well understood for CV disease.
All the cost-effective primary prevention interventions should have been implemented as far as practicable.	Extensive public health initiatives are already in place to reduce incidence.
There should be a simple, safe, precise and validated screening test.	TASCFORCE is investigating this. BNP is simple, safe and cheap and is being assessed as a stratifier to determine who would undergo more intensive imaging.
The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.	TASCFORCE will help answer these questions for BNP and imaging parameters. Additionally biomarkers discovered in the future can be validated using stored samples.
The test should be acceptable to the population.	Acceptability of MRI being assessed by TASCFORCE.
There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.	Would be decided depending on study findings.
There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	Established evidence base for primary prevention (eg with statins).
There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.	Would be decided following study findings.
Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.	There already exists a framework to treat those at increased risk of CV with primary prevention. A screening programme aims to improve how those at increased risk are identified.

Continued on next page.

Table 6.2 continued

There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	Evidence that the programme reduces mortality would need to be assessed at a later stage if it was shown to be effective in determining risk. The concept of CV risk is widely used in clinical practice already.
There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	Would need to be assessed if the method/blood test is shown to be efficacious.
The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).	
The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.	Would need to be assessed if is shown to be efficacious.
All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.	
There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.	
Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.	
Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.	
Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.	

Criteria relating to genetic mutations have not been included.

Follow up for events is by record linkage. This has the dual strengths of cost-effectiveness and potentially reduced attrition. Data on a wide range of clinical activity (such as hospital attendances (including diagnoses), procedures, prescribing and deaths is routinely collected across Scotland, whereas in England such a wealth of information is not as easily available. This data has been (and will continue to be) anonymously linked using their unique community health index (CHI) number for all participants at regular time intervals allowing investigation of a wide variety of outcomes to be followed prospectively. As the vast majority of healthcare is provided by the NHS and almost every participant has a registered GP (who provides the majority of prescriptions) follow up data is likely to be complete, although in England it will be difficult to obtain any data bar death. However Tayside Scots tend to stay in Scotland so it is hoped this will not impact too greatly on follow up. It also does not rely on recurrent study team contacts with participants. This latter approach would be more costly (in terms of both time and finance) and has greater potential to lead to attrition as participants lose contact with the study team.

Weaknesses

The use of the ATPIII score to predict risk means the study has lagged behind developments in clinical practice: the ASSIGN score and inclusion of total cardiovascular risk (beyond coronary heart disease) became the recommended tool during the course of recruitment. Although this difference in practice has resulted in some participants being recruited who would otherwise be excluded and vice versa reclassification only affects a minority of the total participants. The comprehensive collection of baseline data has also facilitated calculation of ASSIGN scores so correlations and predictions can also be analysed with respect to this risk prediction tool. This will allow us to compare efficacy of the respective scores as events occur.

The introduction of glucose testing partway through recruitment meant that it could not be used to exclude those with undiagnosed diabetes. Additionally because a single

elevated random glucose level in the absence of symptoms of diabetes was not sufficient to diagnose diabetes it was not possible to exclude diabetes at the single recruitment visit. Therefore it is possible that a small number of people with undiagnosed diabetes (which is associated with increased CV risk) were recruited to the study as the condition was not recognised and incorporated in the CHD risk prediction. However with the analyses of the blood sugar of the whole population we will have all the random glucose results in due course, and will be able to determine if a formal diagnosis of diabetes is ever made, using record linkage. Additionally analysis of HbA1C from frozen blood samples could now be used to exclude diabetes retrospectively.

Funding and scanner time resource constraints meant that only those with a higher than median BNP were scanned. Although this is in keeping with the hypothesis that a higher BNP identifies a group with an increased CV risk who merit further investigation and assessment of cardiovascular parameters it would have been helpful to image those with a lower BNP. This would have allowed comparison of the imaging markers between those with higher and lower BNP levels and would have led to accurate determination of normal ranges and distributions of cardiac and angiographic parameters for a normal “low risk” population. Imaging of only those with a higher BNP may have led to a biased population being imaged particularly if the hypothesis that increased BNP reflects cardiovascular disease. As a result determination of “normal” imaging parameters from this population has to be interpreted with caution. Any correlations between imaging variables and BNP are likely to be attenuated as the distribution of BNP in the imaged population has been artificially narrowed. Additionally the ability of LVM to predict cardiovascular disease was used as the primary endpoint but less than half of the recruited participants had an MRI scan. This will have resulted in decreased ability to demonstrate the endpoint but it is anticipated that with time as more events occur the potential to show any association will increase.

Although a sub-population of participants of South Asian ethnicity was recruited the remainder of the population were not fully characterised in terms of ethnicity. The ethnically heterogeneous population will limit the assessment of the effect of ethnicity on cardiovascular risk and normal imaging parameters. However with the positive enrolment of people of South Asian origin we believe the population better represents the Scottish population as a whole than other studies which did not make this effort to positively recruit. Other studies have demonstrated significant differences in cardiac structure[182, 184] and remodelling[269] but not function[180] between different ethnic groups. Better characterisation of ethnicity would have allowed normal values to be accurately described for different ethnic groups allowing results to be personalised. This is particularly important for LV mass as this is a parameter that has been shown to be different in different ethnic groups and is the primary outcome of the study. The collection of data about ethnicity would also have allowed investigation of behaviour patterns with screening programmes: for example are those from different ethnic groups more or less likely to engage in screening programmes or undergo MRI scans. However as the main aim of this study is to determine if imaging biomarkers and BNP are able to predict CV events the behaviour aspect is a secondary issue and could be investigated in future studies if MRI is found to be efficacious.

The blood tests for cholesterol were random rather than fasting samples. Additionally 323 (7.3%) of cases had LDL measurements missing, the majority of which were because the level could not be calculated because of a triglyceride level above 4.51 mmol/l or less than the assay's lowest threshold of 0.51mmol/l. This means the data is not missing at random, but is related to the level of triglycerides. Because the reason for missing data is that it could not be calculated it was decided that replacement with multiple imputation would not be appropriate as the best predictors of the values would be the same values that are either not characterised fully (i.e. below the assay detection threshold) or at a higher level which is known to not correlate as well with LDL. It must be recognised however that this means the unavailability of LDL values is

in a population biased by having either very high or very low triglyceride levels. This will have had an impact on multiple regression analyses. It is possible that LDL analyses could be performed on the stored samples using newer assays that are not limited by triglyceride levels but as a great deal is already known about the association of LDL with CVD this is unlikely to add a great deal to the literature.

Although follow up by electronic record linkage is comprehensive and has the strengths outlined above it could also lead to false conclusions. This is particularly the case with prescribing data. Many medications have multiple indications as discussed earlier. For example a prescription for aspirin could be as secondary or primary prevention for cardiovascular disease or as an analgesic. Therefore prescription of many medications that can be used for cardiovascular disease does not necessarily mean they are prescribed for this reason. It can be difficult to determine the reason for prescriptions in all cases which limits the use of this data to draw firm conclusions. However further analysis including the doses of medications could help differentiate use for cardiovascular disease from other indications.

There are also limitations to using the wide range of cardiovascular events some of which are often poorly coded or can be “diagnosed” without any hard clinical evidence to support them (such as “angina”). The aim was to capture all events however it is accepted that this will increase sensitivity for events at the expense of specificity. This is one of the drawbacks of electronic record linkage follow up where it can sometimes be difficult to get further confirmatory information to corroborate diagnoses. However the follow up information is in the form that can be filtered to only include major adverse cardiovascular events.

6.3. Usefulness of screening for incidental findings

6.3.1. Increased cardiovascular risk

The screening process for recruitment to the study identified a significant number of people who had previously unidentified increased cardiovascular risk or hypertension that would merit further investigation or treatment. 146 (2.9%) and 291 (5.8%) of the 5015 people screened were found to have a high predicted cardiovascular risk or hypertension respectively. This compares to positive faecal occult blood test rates in the pilot bowel cancer screening programme of 1.6% to 2.1%[240] and a recall for assessment rate following mammography of approximately 4% in the breast cancer screening programme.[270] This highlights the importance and usefulness of screening for increased cardiovascular risk to allow early intervention to reduce the risk of future cardiovascular disease. This is encouraged via the quality outcomes framework (QOF) embedded in GPs' contracts. The section on primary prevention of CVD currently requires those with a new diagnosis of hypertension and who have a CVD risk assessment score greater than 20% in the previous 12 months be on a statin and those with hypertension to be given lifestyle advice (increasing physical activity, smoking cessation, safe alcohol consumption and healthy diet).[271] Compliance with this standard in Tayside in 2013/14 was 96.3%[272] suggesting that of those identified to be at risk appropriate management was being instigated. However the QOF does not drive the routine assessment of CV risk in those at a younger age and relies on them attending their GP practice to have risk factors measured. Our finding of a large number of people with previously unrecognised increased risk shows there is room for improvement and opportunity to improve how screening for risk is performed. For example our method of proactively going to screen people may augment practice based screening.

Of those who failed screening 171 (42.5%) (172 (42.5%) when aspirin excluded) received a new prescription for cardiovascular medication following their screening visit and during the follow up period. The rate of prescription and odds ratio of receiving a prescription in those who failed screening was significantly higher than the eligible study population. This probably reflects the increased cardiovascular risk in this group and it would be expected that they may be prescribed medication at some point during follow up if the increased risk was detected by their GP. However significant number of these were in the first few months after screening (the lines on the Kaplan Meier analysis are steeper initially) suggesting that the screening visit may have prompted the new prescription and suggests pro-actively screening people may be beneficial in improving treatment rates for cardiovascular risk factors compared to opportunistic screening at GP surgeries. The median time to receiving a prescription was 204 days so half those who failed screening and received cardiovascular medication had received a prescription in just over 6 months.

Those who failed due to hypertension had a shorter time to first prescription on Kaplan Meier analysis than those who failed due to high cardiovascular risk. Because BP was checked before cardiovascular risk was calculated some who failed screening due to hypertension may also have had a high overall CV risk but they were recorded as being hypertensive in preference. High cardiovascular risk is often due to a combination factors (for example smoking, blood pressure and lipid profile) potentially without one measure being significantly elevated. Therefore people with high predicted risk but not hypertensive may have elected to try lifestyle changes initially (eg smoking cessation, exercise or dietary modification) rather than start on medication. Those with just hypertension may perceive this risk as being something that is not as amenable to lifestyle modification and as a single risk factor may start medication for it instead. Lipid modifying drugs were prescribed to proportionately more people who failed screening due to high cardiovascular risk compared to those who were hypertensive as would be appropriate clinically. Also as would be expected antihypertensives (particularly

angiotensin converting enzyme inhibitors, calcium channel blockers, beta blockers and thiazide diuretics) were prescribed more to the hypertensive group. This would largely be in keeping with guidelines. Despite this only half of those we found to be hypertensive were subsequently prescribed antihypertensives. This may be because BP was not found to be elevated when rechecked by the GP or with ambulatory monitoring, or because lifestyle measures such as exercise or weight loss were used instead of medication in others. The fact that they had previously undetected hypertension may also reflect a reticence in some to attend their GP and be reviewed.

There was no statistically significant effect of exposure to CV medication on the cardiovascular event rate. This is probably due to the relatively low incidence of cardiovascular events in the follow up so far meaning power was not great enough to show any effect. As follow up for events continues this difference may become significant in the future. The evidence for primary prevention for CV disease shows that the benefit accrues with time therefore emphasising the need for a longer follow up time.

6.3.2. Non-cardiovascular findings

A small number of incidental findings of anatomical abnormalities and masses were picked up by MRI scan (n=32, 2.1% of those scanned). This generated an increase in clinical activity in the form of supplementary imaging and or clinical review however is necessary to either investigate if further action or treatment is necessary or to reassure the participant and staff of the benign nature of a finding. One participant was found to have a malignancy. Although the detection of an otherwise unknown malignancy is potentially beneficial by allowing earlier detection of a cancer, participants in the study weren't routinely counselled pre-scan about this possible finding. Despite the low rate of incidental malignancy (only one participant), 32 (2.1% of those imaged) required further investigation or assessment (including imaging in some cases) to investigate the initial incidental finding further which may have caused distress or anxiety to

participants. It would therefore be important in clinical practice or in future trials to discuss the potential for such incidental findings when obtaining consent for imaging in clinical practice.

6.4. Baseline results

6.4.1. Risk factors and BNP

The BNP levels in our population were not dissimilar to those found and proposed to be reference ranges in a sub-population of the Framingham offspring cohort free from cardiovascular disease, hypertension and diabetes although they only quote mean values so direct comparison is impossible.[140] BNP levels were significantly higher in women compared to men as demonstrated in previous studies (using both BNP and NT-proBNP)[92, 139-141, 146] justifying our use of gender specific medians for deciding whether participants were offered an MRI scan. The median results for men and women were also close to the cut-offs used (determined earlier in the study) for allocating to the MRI/BNP group. Notably the vast majority of participants had a BNP level below the threshold of 100pg/ml used for the potential diagnosis of heart failure. Only 2 men and 14 women had a BNP reading above this level and the 99th percentile for both genders was below this level. The women with a BNP greater than 100pg/ml were older and had a slightly higher predicted risk using the ATPIII and ASSIGN scores (although they all still had a predicted CHD risk less than 10%). Apart from age there was no significant difference in any individual CV risk factor measured. The 2 men with a BNP >100pg/ml had a higher predicted risk using both the ATPIII and ASSIGN scoring algorithms but due to the small numbers the differences were not as statistically significant and no individual risk factor measured was significantly different. These findings may suggest that because women on average have a higher BNP level the same threshold is less able to identify those at increased risk than in men. The findings also suggest that the increased level may just be a marker of age (which is a

risk factor for CVD). This provides evidence for the need for age and gender specific thresholds and normal values for BNP as discussed in more detail below.

The reasons for women having higher BNP levels have been explored in a study of a population free from cardiovascular and cardiovascular medication and in who LV failure (including diastolic dysfunction) had been excluded by echocardiogram.[139] Higher BNP levels were not explained by gender related differences in blood pressure, renal function or cardiac structure; although there were associations between gender and renal function and blood pressure these were confounders and did not remain associated when age and gender were corrected for. The higher BNP level may be related to oestrogen status as BNP levels were higher in women using HRT.[139] The differences in BNP between genders may also be due to a greater degree of stretch in the hearts of women because they have smaller hearts (both mass and volumes). However as the stroke volumes and cardiac output are also lower in women there is little to support his theory in our findings.

Those allocated to the MRI/BNP group (i.e. those with a greater than median BNP) were older, had a slightly higher systolic BP, lower heart rate, higher HDL, lower triglycerides, lower BMI, greater height, lower waist circumference, contained fewer current smokers and higher ASSIGN score and more people with an intermediate 10 year CHD risk score (calculated using the ATPIII algorithm). These latter two findings are reassuring as they indicate that BNP level may be a marker of an individual's risk and support our use of it for this purpose. Men with a BNP reading in the 4th quartile were older, had a lower diastolic BP, lower heart rate, higher HDL, lower triglycerides, lower BMI and higher 10 year cardiovascular risk compared to those with a lower BNP. Women with a BNP in the 4th quartile were also older, had a lower heart rate, higher HDL, and higher 10 year CHD risk but also had a lower proportion of current smokers (probably driving the lower numbers of current smokers in the MRI/BNP group as a whole as mentioned above), higher proportion of never smokers, higher systolic BP but

no significant difference in triglycerides, diastolic BP or BMI. The differences in the variables between groups noted above from the univariate analysis could be due to genuine physiological effects, the statistical effect of performing a large number of univariate analyses and therefore “finding” differences by chance that do not exist in reality (type 1 error) or because some risk factors dominate cardiovascular risk leading to biases in other risk factors to counter the dominant ones while still ensuring overall cardiovascular risk is low enough for people to be eligible for the study. Possible reasons for the differences we found are discussed further below. Using a stepwise multivariable linear regression analysis age and female sex along with ex-smoking status, lower heart rate, lower total cholesterol and higher HDL remained independent predictors of log10BNP level suggesting these correlations are genuine after correcting for confounders. It is likely therefore that current smoking status is not an independent predictor od BNP level as suggested by the univariate analysis but more likely due to confounding from other variables. We did not include CHD risk in the multivariable analysis as it is derived from the other CV risk factors that were included. Of note BMI, triglycerides and lower waste circumference were not correlated in this analysis. This may be because body size (measured either by BMI or by waist circumference) is associated with other cardiovascular risk factors (such as lipid profile and blood pressure) so the effect of these is reflected in those other factors. Triglycerides were within “normal” range for most people so the range of values recorded may have been too small to allow any correlation to be seen.

Increasing levels of BNP with age are well recognised.[139-141] The exact mechanism for this association remains unclear; although renal function and age related changes in cardiac size could have some influence on levels, the effect of age on BNP is independent of renal function, atrial volume, LV dimension and LV mass.[139] Age related alterations in production, secretion or degradation may be responsible. Decreasing cyclic guanine monophosphate (cGMP) to BNP ratio with increasing age has been demonstrated[273] suggesting an attenuated biological effect of BNP with

increasing age requiring higher levels of BNP to have the same effect. Natriuretic peptide C receptor levels, involved with clearance of BNP, are also reduced with ageing[274] suggesting a reduced rate of clearance of BNP. The large combined impact of gender and age has led to suggestions that age and gender specific BNP levels should be adopted if BNP or NT-proBNP is being used for screening.[141] Our findings very much support this and could be used to derive “normal” age and gender specific BNP parameters.

The inverse association between heart rate and BNP could be caused by the increased filling time that results from a lower heart rate causing increased myocardial stretch which stimulates release of BNP. Those with a higher BNP could paradoxically be fitter and therefore have a lower resting heart rate. This is supported by the fact that a higher BNP was associated with lower waist circumference in men and lower BMI in men and women. It could also reflect a physiologically increased LVM due to exercise: a lower heart rate may be a marker of exercise participation which could increase LVM. However as discussed later BNP was not independently associated with LVM which makes this explanation less likely. It may be that BNP within this “physiologically normal” range reflects differences in healthy physiology rather than pathology.

The higher ASSIGN scores and greater proportion of people with intermediate CV risk in those in the MRI/BNP group is in keeping with results from a study of patients with diabetes but no pre-existing CVD where log10 BNP was positively correlated with Framingham risk score.[134] This lends more support to BNP being a marker for global CV risk even though association with individual risk factors is less marked. It is likely that age and gender are the greatest drivers of the predicted cardiovascular risk (and therefore potentially BNP level) in our population therefore overshadowing the other differences in the individual contributors to cardiovascular risk. The fact that cholesterol and triglyceride levels were not significantly elevated above clinical “normal” values in either the MRI/BNP or MRI group supports the theory that they are unlikely to be

contributing significantly to the cardiovascular risk profile and potentially BNP level in this low and intermediate risk group. Although statistically significant differences in the HDL and triglyceride levels do exist between those with higher and lower levels of BNP the magnitude of differences is small and therefore unlikely to have a large effect on cardiovascular risk when compared to age and gender. The lower triglyceride and higher HDL levels in those with higher BNP results (the opposite to what would be expected in those at higher risk) may be due to a biased population brought about by effect of age. Because age is a variable used in the CHD prediction those who are older were more likely to be excluded due to high CHD risk (see earlier discussion) meaning those older people who were eligible may have had more favourable other risk factors to “compensate” for their increased age. As BNP is also increased with age the group with higher BNP includes a skewed higher age group with this more favourable (other than age) risk factor profile.

The reasons for lower BMI, lower waist circumference and lower proportion of smokers in the MRI/BNP group is less clear as these findings may be expected to be associated with a lower cardiovascular risk. Lower BNP levels in obese compared to non-obese people have been demonstrated in both heart failure[275] and heart failure free[276] populations. The reasons for this are not fully understood but an abundance of natriuretic peptide clearance receptors in adipose tissue[277] may increase the rate of removal of BNP in those who are overweight or obese and therefore have a higher BMI and waist circumference. As the multivariable regression analysis did not show that BMI or waist circumference were independently associated with BNP, it is possible that body size is merely a marker for other cardiovascular risk factors.

In summary, higher BNP levels appear to be associated with female gender, older age, and increased predicted CHD risk although associations with other individual risk factors such as BP, lipid profile and obesity are conflicting or in the opposite direction to what would be expected possibly because of unintentionally skewed populations

caused by the effect of age on both cardiovascular risk and BNP level. As the main aim of the study is to determine if BNP aids prediction of future cardiovascular events beyond the measurement of traditional cardiovascular risk factors the association and exploration if BNP is associated with actual future events is more important in terms of clinical applicability. As follow up continues and cardiovascular events accumulate to a significant level investigation of whether BNP predicts CV events will be possible. As the vast majority of people have “normal” levels of BNP it may be that there is a threshold above which BNP may be predictive of events as shown in other studies albeit with different study populations.[133] Our findings support the results of other studies that gender specific BNP levels should be used as age seems to be an independent predictor of its level. However as CV risk increases with age means it may not be desirable to correct completely for this risk factor. It is also possible that BNP is acting as a surrogate marker for age and may not add any further prognostic value within a normal range.

6.4.2. Cardiac imaging baseline results

Left ventricular mass (LVM) was significantly higher in men than women supporting the results of other studies that have measured LVM using MRI.[177, 183, 185, 187, 256-258, 260, 261] There was a strong correlation of LVM with height, weight and body surface area. All these measures of body size were different between men and women but the gender differences in LVM persisted even after indexing by each of these parameters. This also supports the findings of the other studies where LVMI is different between men and women when corrected for either height or body surface area. The persistence of differences when corrected for body size suggest that gender differences are not solely due to different body sizes and height but are genuine gender differences. These could be due to different metabolism, hormonal effects or genetic differences.

The mean LVM and LVMI values in our cohort are similar to those reported by other studies that have used steady state free precision (SSFP) imaging sequence MRI to determine LVM in a healthy population without cardiovascular disease and free from hypertension, high cholesterol or treatment.[177, 259] The mean LVM in TASCFORCE was 128.9g and 87.1g for men and women respectively compared to 134g and 98g for 20-80 year old men and women in the pooled estimate of LVM from three studies that have used SSFP sequences with a 1.5T scanner. So far no-one has published normal values for SSFP using a 3T scanner (as used for TASCFORCE). The four studies combined have only studied 1140 people (493 men and 647 women) compared to the 1515 (577 men and 938 women) imaged in TASCFORCE making our population significantly larger than any other single study. Our values for LVM indexed for body surface area are also similar for men but slightly lower for women compared to the pooled results. Alfakih et al quote normal values for a subgroup aged 40-65 (more similar to our population than the pooled results) which are very similar to our results for both LVM and LVM indexed for BSA for both men and women.[256] This suggests that the difference in women may be caused by the inclusion of younger people in the pooled results. Our results for LVM and LVMI (for BSA) were also similar to the subgroup of those aged 35 or older in Hudsmith et al's population.[257]

We also found that LV end diastolic volume, end systolic volume, stroke volume and cardiac output were all significantly higher in men compared to women and ejection fraction was higher in women. These differences remained when the parameters were indexed for height, $height^{1.7}$, $height^{2.7}$ or BSA except for stroke volume corrected for $height^{2.7}$. Similar gender differences have been reported previously. End diastolic and end systolic ventricular volumes, stroke volumes and ejection fractions are similar to the pooled results[259] and particularly those of a similar age and when indexed for BSA.[256, 257] There are some differences between TASCFORCE and the other SSFP MRI studies quoting normal values. They all included papillary muscles in the left ventricular mass whereas we excluded it and included it in the LV cavity volume.

Papillary muscle has been noted to account for about 9% of total LV mass[278] so it would be expected that our volumes would be slightly higher and masses slightly lower than others. We also only imaged those with a BNP greater than the gender specific mean so do not truly represent the whole population. However the vast majority of participants had a “normal” BNP and the only significant difference in LV parameters with a higher BNP was slightly decreased cardiac output as discussed below. Therefore the results LV are likely to represent the population as a whole.

Other studies have used turbo gradient echo (TGE) MRI sequences for cardiac imaging. When directly comparing the TGE with SSFP sequences in the same patients TGE has been shown to produce higher values for mass and lower values for LV cavity volumes compared to SSFP.[256] Improved border definition is possible with SSFP which could lead to differences in endocardial border definition between the 2 sequences. This explains why the values for LVM and LVMI are higher and left ventricular volumes (both raw and indexed for body size) are lower in a low risk group of the MESA study,[182] in the Framingham Heart Study offspring cohort[183] and in Marcus *et al’s* study of “healthy” volunteers in the Netherlands[260] compared to TASCFORCE.

The differences in parameters obtained by the different imaging methods mean that measurements using the two techniques are not interchangeable and reference values for each technique are required. As well as for the mass and volume measurements this also has implications for the calculation of LVM/LVEDSV which is used to determine concentric LV remodelling.

In addition to the techniques there are also differences in the populations between the various studies. Marcus *et al*’s population was younger (mean age was 22.9 and 21.9 years for men and women respectively) and was taller and leaner whereas the Framingham cohort had a similar age range and body composition to TASCFORCE.

Ethnicity may also play a role. Although we did not collect detailed ethnicity data for the TASCFORCE participants the local population is predominantly white European with some of South Asian ethnicity so the study population is likely to reflect that. In comparison the MESA study included a significant number of African-American, Hispanic and Asian-American people.[182] Although they did not find a statistically significant difference in LVM or LVMI (for BSA) between the different ethnic groups except between Asians and the other groups the mean values for African-Americans were higher than for other groups and for Asians were lower which will have influenced the results. The three main studies that have used SSFP were all European[256-258] but ethnicity was not reported so it is not possible to explore ethnic differences. Another factor that may influence LVM in different populations are exercise: increased level of exercise produces physiological increase in LVM rather than a pathological increase due to hypertension or intrinsic cardiac disease. From the data available it is not possible to compare exercise levels between the different study groups to determine if this is a factor contributing to the different results between studies.

We have used a variety of measures of body size to index left ventricular measures. Although still significantly different between genders the magnitude of difference is less when allometric indices are used ($height^{1.7}$, $height^{2.7}$) compared to ratiometric indices. As discussed earlier use of allometric indices is theoretically superior.

The higher LVM and LVMI in men compared to women is opposite to the difference in BNP results where women had higher levels. For this reason associations between LV measures and BNP and baseline factors were analysed separately for men and women. As raised BNP is associated with left ventricular hypertrophy and left ventricular failure it may have been expected that either BNP would be correlated with LVM or a raised BNP (for example above a certain threshold) would be associated with either higher LVM, decreased LV function or both. This was not the case. BNP was weakly correlated with end diastolic volume and stroke volume (both raw and indexed

for body size) in men but not with any other left ventricular measures. BNP was not correlated with any measures in women. The correlations with end diastolic volume and stroke volume in men could be due to increased stretch brought about increased ventricular filling. This in turn may be due to a decreased heart rate leading to increased filling time. Our finding of an inverse correlation between heart rate and left ventricular mass and left ventricular volumes in men supports this. The lack of correlation between LVM or LVMI and BNP may be because LVM and BNP levels are "normal" in the vast majority of participants as this is a healthy population. However even when we performed analyses looking at different thresholds for "abnormal" BNP levels we did not demonstrate significant associations with increased left ventricular mass. When thresholds of 90^{th} and 95^{th} percentiles of BNP were investigated to identify those with a higher BNP compared to the rest of the normal population the differences in LV parameters were still not significant between those with a higher and lower BNP except for a decreased cardiac output with higher BNP. As the ejection fractions and stroke volumes were not different the lower cardiac output is probably a product of a decreased heart rate with higher higher BNP rather than cardiac function. There was no significant difference in BNP level when LVH in our healthy population was defined as an LVM greater than 2 standard deviations above the mean (gender specific). BNP was also not different between those with and without concentric LVH defined as LVM/LVEDV greater than 2 standard deviations above the mean. As LVM mass was negatively correlated with age in men whereas BNP increases with age any increase in BNP with increased LVM may be hidden by the age related decrease in LVM. An alternative method may be to use age and gender specific reference ranges for BNP to see if that identifies LVH. However in a multivariable regression analysis BNP was not an independent predictor of any LV parameters suggesting that in this healthy population, where BNP is within the normal range, BNP is not genuinely not associated with LVM or LVMI. This supports evidence from the Dallas Heart Study where BNP was not able to accurately identify people with LVH or LV systolic dysfunction in a young and healthy population.[262] A limiting factor in our analyses is that the range of

BNP levels is relatively narrow as only those with a higher than median BNP were imaged. If those with a lower BNP had been imaged a wider range of BNPs would have been included.

Age was weakly but significantly inversely associated with LVM and LVMI (except when indexed by height$^{2.7}$) in men but only with LVM and LVM indexed by height in women. These associations persisted in a multivariable regression model suggesting that the association may be independent of other changes in CV risk that accompany age. Age was also associated with decreasing LV volumes, stroke volume and cardiac output in both men and women which persisted when corrected for other variables in the multiple regression models. Ejection fraction was weakly positively correlated with age in both sexes but only in women when corrected for other variables. Natori *et al* report an inverse association between age and LVM (but not LVM indexed for BSA) and LV volumes in men.[182] They however found no association between LVM or LVMI with age but an inverse association of left ventricular volumes with age in women. Maceira et al also reported that mass and volumes (both raw and corrected for BSA) decrease with age in men but only volumes and not mass do in women.[258] The reduction in myocardial mass with age could reflect genuine reduction in mass due to decreased activity as people age. This could also account for the decreased stroke volume and left ventricular volumes. It could also reflect the increasing likelihood of having cardiovascular disease or increased cardiovascular risk with increasing age. Those with higher LVM or volumes may have been excluded from the study due to increased cardiovascular risk or hypertension so the older participants who were imaged were a biased sub-population of relatively healthy older people. Because age plays a significant part in the CHD risk prediction those who were older and eligible may be a population with a lower BP to compensate for an increased age.

Systolic BP was positively associated with LVM and LVMI in both men and women and the association remained when adjusted for other covariates in the regression model

(although the association was only weak). Diastolic BP was also associated with LVM and LVMI in both sexes on univariate analysis but only in women on multivariate analysis. The association of systolic BP and smoking with LVM supports the findings of the MESA study[187] although they found a stronger association between LVM and BP in men whereas we found a marginally stronger correlation in women. The association with systolic BP would be expected as increased BP results in increased cardiac work and is known to lead to hypertrophy although the strength of association we demonstrated was not as large as may be expected. Current smoking was independently associated with LVM and LVMI in women but not men. The association with smoking is also expected as smoking increases myocardial work, increases BP and acutely increases the stiffness of peripheral arteries.[279] BMI was moderately associated with LVM and LVM indexed for height in both univariable and multivariable anaylsis. The lack of or reduced association with LVM indexed for BSA is likely to be due to the association of BSA with BMI meaning the increased BMI is corrected for when indexed for BSA. The association of BMI with LVM would be expected as increased weight results in increased metabolic demand and therefore cardiac demand and is known to be a risk factor for cardiovascular disease. The stronger association of smoking and blood pressure in women compared to men may again reflect the different risk factor profile in the male population caused by the effect of male gender on risk discussed previously.

In univariate analysis heart rate was negatively associated with LVM and LVMI in men but only LVM indexed for BSA in women. However in the multivariable models heart rate was independently associated with LVM and all LVMIs in both genders. The reason for this is unclear as decreased resting heart rate would be expected to be associated with better cardiovascular health and therefore decreased LVM. It is possible that the correlation is due to the presence of physiologically increased LVM due to exercise (which would be associated with a lower heart rate) rather than pathologically increased LVM. This is particularly the case as the study population was

a low CV risk group therefore likely to be a healthier fitter group where pathological changes are less prevalent. Lower heart rate could be acting as a surrogate marker for exercise. Heart rate was also inversely associated with end diastolic and end systolic volumes in both men and women. This hypothesis would be in keeping with a previous study where higher levels of intentional exercise were associated with greater left ventricular mass, end diastolic volume and lower resting heart rate.[280]

The presence of exercise related physiological changes in LVM may explain why LVM and LVMI were not correlated with predicted CHD risk in men. However in women LVM and LVMI were associated with CHD risk which may suggest increased LVM was more pathological in women compared to men in our study. However the association was only weak. The MESA and Dallas Heart study groups have previously reported that LVM is more strongly associated with the incidence or risk of heart failure than CHD or stroke.[181, 191, 281] However greater left ventricular mass has been associated with low short term/high lifetime risk compared to low short term/low lifetime risk[186] so it may reflect lifetime risk (that we have not calculated) rather than short term risk.

LV mass/left ventricular end diastolic volume (LVM/LVEDV) ratio is commonly used as a marker of concentric cardiac remodelling which is a pathological change. This was correlated with 10-year CHD risk in men and women. In women the correlation was stronger than for LVM or LVMI. In multivariable analysis LVM/LVEDV showed a positive association with systolic BP, and current smoking status in both men and women and additionally age, heart rate, diastolic BP, LDL and waist circumference in women only lending further support to the argument that this may be a better index of pathological changes to the myocardium. The positive association of heart rate with LVM/LEDV (compared to the inverse correlation seen with LVM and LVMI) suggests this measure may differentiate those with pathologically increased LVM from those with a physiologically increased LVM. The MESA study reported that LVM/LVEDV after adjustment for risk factors was associated with incident stroke and incident CHD[181,

191] again showing this may be a better measure of cardiovascular risk than LVM or LVMI and suggests that remodelling is a more important factor than mass alone.

Cardiac volumes (end diastolic, end systolic and stroke) all decreased with age in both men and women. Age remained independently inversely associated with volumes on multivariable analysis. This may reflect decreasing physical activity with increasing age. Volumes were also inversely independently associated with heart rate in both men and women possibly reflecting a healthier lifestyle (causing a lower resting pulse). End diastolic volume, stroke volume and cardiac output was independently associated with BMI in both men and women (plus end systolic volume in men). This was most likely driven by the increased metabolic and circulatory demands in those who have a greater body mass. Ejection fraction was only independently associated with ex smoking status in men but with age (strongly) and systolic BP in women. The lack of independent associations in men may be caused by the relative healthy condition of men due to the biased population as discussed previously. Additionally the men appear to have more physiologically affected hearts (eg due to exercise) than the women as demonstrated by the differences in concentric remodelling discussed earlier. The associations with age and systolic BP in women would be expected as these are both cardiovascular risk factors. Women with a BNP >100pg/ml (the diagnostic threshold for heart failure) had a lower ejection fraction than those with lower BNP. This is in keeping with the diagnostic use of BNP for heart failure and shows a significantly elevated level can detect decreased cardiac function. Interestingly ejection fraction was weakly associated with predicted CHD risk in both men and women. This is the opposite direction of association to what would be expected as cardiovascular risk would be expected to be associated with impaired cardiac function. This may be a “statistical anomaly” due to looking for multiple associations or could again be due to the prominent effect of age on cardiovascular risk resulting in a population where older people are actually healthier (including having healthier hearts) to compensate for their age and still allow inclusion in the study.

6.4.3. MRA baseline results

The vast majority of arterial segments scanned produced images suitable for analysis with only 0.6% of the images unsuitable. This provides further evidence that the technique is technically suitable to be used in screening. As would be expected in a healthy population the vast majority of segments were normal with no stenosis and of those that were abnormal most only had a mild stenosis (<50% of lumen). Only a very small number had an aneurysm. The highest abnormality rate was found in the coeliac artery with an abnormality rate about 75% higher than the next most affected segment (the abdominal aorta). The coeliac artery also had a higher proportion of more severe luminal stenosis (50-70% and 70-99%) than any other segment. This is likely to be due to an anatomical variant as the artery runs under the median arcuate ligament in a significant number of people which can result in compression of the artery particularly during expiration and can produce arterial narrowing.[267] This is a limitation of luminography where the vessel wall is not imaged as it is not possible to distinguish the anatomical variant from atherosclerotic disease. The coeliac artery also had the worst inter-observer correlation possibly reflecting the difficulty interpreting the images due to the anatomical abnormalities described above. For this reason whole body atheroma scores were calculated both including and excluding the coeliac arteries for illustrative purposes but all correlations with baseline risk factors and other imaging variables have used the scores without the segment included.

When the coeliac artery was excluded 766 (50.6%) of people had normal standardised atheroma scores. Of those with abnormal scores 45% had just one segment affected although many people did have stenosis affecting more than one segment suggesting possible widespread subclinical disease. With the coeliac artery excluded the most commonly affected segment was the abdominal aorta where most of the abnormality was minor (less than 50%) followed by the left subclavian and right and left iliac arteries. As these are all vessels with a relatively large lumen and large flow it is possible that subclinical disease develops here before it does in smaller vessels.

However because they are larger vessels atheroma would have to be become quite thick before it caused significant stenosis and therefore clinically evident disease (a similar sized plaque in a small artery would cause proportionally more luminal stenosis). As follow up continues it will be interesting to see if such abnormality in large vessels is prognostically important. The standardised atheroma scores were very positively skewed as would be expected for a disease free and low risk population where the majority of people have normal vessels and only a minority have more extensive disease.

The standardised atheroma score was positively associated with age, systolic blood pressure, total cholesterol, LDL and predicted 10-year CHD risk in men and women and additionally with triglycerides in women and inversely with SIMD in men. When adjusted for other baseline factors in a multivariable model there was an independent association with age, systolic BP, ex-smoking status, heart rate, current smoking status and inversely with SIMD decile. The strongest association was with age suggesting this is the greatest driver of the association with predicted CHD risk although the independent association with blood pressure, smoking status and SIMD in the regression model suggests that age is not the only factor driving the association with CV risk. Resting heart rate may be a surrogate marker for exercise which could explain its positive association with SAS. When those with a greater than 80^{th} percentile of SAS were compared with those with a lower SAS age, systolic blood pressure, total cholesterol, LDL and predicted CV risk score were all higher in those with the greater SAS. This lends further support to the hypothesis that cardiovascular health is reflected in the stenosis seen on MR in the TASCFORCE study and is supported by findings from other studies. In the PIVUS study of 70 year-olds a similar atheroma score was associated with Framingham risk score, male gender, cigarette pack years, HDL, systolic and diastolic blood pressure and cigarette pack years.[208] Their participants were all aged 70 so it was not possible to examine correlation with age however this showed that in that age group atheroma burden was still associated with

cardiovascular risk independent of age. Their participants were of mixed risk factor profile (for example including people with hypertension). The older age and different risk factor profile is likely to be the cause for the higher level of atheroma detected in the PIVUS study (they detected atherosclerotic changes in 68% of participants)[211] compared to TASCFORCE. A whole body magnetic resonance angiography based score has also been associated with age, male sex and coronary artery disease status in a population of patients with long-standing diabetes.[282]

The PIVUS group's scoring system was subtly different as outlined above in section 6.2.4. In particular they did not differentiate the degree of stenosis beyond greater or less than 50% (greater included occlusion). In a screening population such as ours the presence or absence of atherosclerosis may be more important than the exact degree of stenosis so a scoring system more similar to the PIVUS score may be more appropriate. This was explored by investigating the percentage of segments per participant with any abnormality. The percentage of abnormal segments was still associated with age, systolic BP, heart rate (women only), total cholesterol, LDL, triglycerides (women only) and predicted CHD risk score suggesting that the more intricate scoring system may not be required. When those with normal arteries were compared with those with any abnormality in any artery those with abnormality were older, had a higher systolic BP, higher total cholesterol, higher LDL, and higher CV risk than those without abnormality giving further weight to the argument that the presence of any stenosis may be as important as the degree of stenosis.

There was no correlation with SAS score or number of affected arterial segments and BNP or any differences in BNP level between those with any arterial abnormality. Because the degree and amount of stenosis in this population is so low it is possible that any stenosis present is not sufficient to increase strain on the heart to stimulate release of the hormone. As with the BNP association with left ventricular measures our analysis is limited by the fact that only those with an above median BNP were imaged.

Therefore the range of BNP in those with SASs is narrower than would be the case in the general population which may have limited the ability to detect significant differences.

Those with an SAS greater than the 80th percentile had a higher LVM/LVEDV than those with a SAS less than the 80th percentile indicating that those with more atheroma burden have greater presence of ventricular remodelling. They also had lower end diastolic and end systolic LV volumes and these cardiac measures were also inversely associated with the SAS. The lower LV end diastolic volume and end systolic volumes in those with higher SASs could reflect early abnormal cardiac remodelling. The increased LVM/LVEDV could be due to increased strain on the heart by the presence of atheroma (or poor vascular health predating the atheroma) or could be due to the shared risk factors for both. However the associations are likely to be affected by age which is independently associated with increased LVM/LVEDV and also the SAS. There is therefore likely to be some co-linearity. There are no published studies examining associations between MRA derived whole body atheroma burden and cardiac MRI derived LV measures making the combination of these techniques unique.

6.5. Primary outcome – ability of BNP and left ventricular mass to predict cardiovascular events and death

At 2 year follow up an equal number of combined cardiovascular events and deaths occurred in both the BNP and MRI/BNP groups with no significant difference in the event rates. The total person years at risk was slightly higher in the BNP group but this group also contained more people so the average years at risk per person was similar between the groups. More cerebral events occurred in the MRI/BNP group whereas more coronary events occurred in the BNP group. The small number of events in the short follow up time so far would be as expected in this population who are predicted to be at low risk of CVD. As a result of the small number of events it is not surprising that

there is no statistically significant difference in event rates between those with higher and lower BNP levels even though the event rate is marginally higher in the MRI/BNP group. As we would expect it is therefore unclear at this stage if BNP is a useful predictor of CV events in this low risk group. As the first projected follow up analyses is at 5 years hopefully the event rate will be sufficient for a meaningful analysis at that time.

The numbers and rates of CV events in those with LVMI (using height, $height^{1.7}$, $height^{2.7}$ and BSA) and LVM/LVEDV ratio were slightly higher in those with measurements above the median compared to those below the median and in the top quartile compare to the lower quartile. However the confidence intervals for the rates are quite wide and overlap. Again this probably represents the small number of events at this stage of follow up. This is exacerbated by the fact that of the 17 events in the MRI/BNP group 10 occurred in people who were not able to tolerate or refused an MRI scan therefore only 7 occurred in people who had scan images. As follow up continues it will be interesting to see if the confidence intervals narrow and the differences between those with higher and lower LVMI become significant. It may be that any increase in CV event rate in those with higher LVM, LVMI and LVM/LVEDV reflects increased CV risk and may not add any further information: LVM and LVMI are associated with increased predicted CHD risk in women however not in men and LVM/LVEDV is associated with increased CHD risk in both men and women. Once more events have occurred as follow up continues multivariable statistical models will need to be used to determine if LVM or LVMI independently adds to the prognostic ability of existing clinical prediction tools.

As discussed above more than half of the events in those who were eligible for an MRI scan (the MRI/BNP group) occurred in those who either declined, were unsafe to scan or were unable to complete a scan due to claustrophobia or technical reasons despite this group being smaller than those who underwent a scan. In a subgroup analysis of

those who were eligible for a scan (MRI/BNP group) comparing those who did and did not complete a scan there was a trend of a higher rate in those who did not have a scan compared to those who did although the low numbers of events make it difficult to draw any firm conclusions. The subgroup (of the MRI/BNP group) who did have a scan had less men, a small but statistically significant lower heart rate, systolic and diastolic blood pressure, and higher HDL compared to those who completed a scan. However the median predicted risks (using both ATPIII and ASSIGN) were not different between the groups. Any difference in rates could reflect the health behaviour of those who were willing to have a scan which would not be picked up directly by the risk scores: were people willing to have a scan more “health conscious” and therefore took a greater interest in their health than those who did not have a scan?

6.6. Ability of whole body MRI angiogram to predict cardiovascular events

The cardiovascular event rate in those with any presence of atheroma had a trend towards being higher compared to those who had no evidence of atheroma however the confidence intervals were wide and overlapping. As discussed above in relation to cardiac parameters this probably reflects the relatively small numbers of events that have occurred so far particularly in those who completed a scan and as follow up continues it will be observed if differences are significant when further analysis is performed at 10 and 15 years follow up. Again it may be that any increased CVE rates associated with presence of atheroma merely reflects the association of increased CV risk associated with atheroma and modelling will need to account for confounding factors to see if the atheroma score adds to the predictive ability of the clinical scores. As follow up continues this will be become apparent.

6.7. Conclusions

The main short term aim of this study was to establish recruitment strategies, and to recruit a population of sufficient size such that defined end points could be used at 5, 10 and 15 years to evaluate their strengths or otherwise to predict CV events. This has been achieved. The phenotypic and genotypic data has been recorded, and tissue samples sored for future analyses. MRI data has also been recorded in detail. Data linkage of the population has been established.

As expected we have not demonstrated the ability of left ventricular mass determined using magnetic resonance imaging to predict cardiovascular disease so early in follow up in a population at low or intermediate risk of CHD. Although those with a left ventricular mass in the upper quartile for their gender had a trend towards a higher rate of cardiovascular events this did not reach statistical significance. This may be due to the low number of events that have occurred so far at this early stage of follow up. As follow up using electronic record linkage continues and further events occur we will establish whether increased left ventricular mass or concentric remodelling predicts or not cardiovascular events in future analyses.

Again as expected we have not demonstrated the ability of presence of subclinical arterial stenosis detected using whole body contrast enhanced magnetic resonance angiography to predict clinical CV disease in the low or intermediate risk population. As with the left ventricular results above it is possible that the low number of events so far has led to a non-significant result and further follow up may show a significant ability to predict events.

We have also not demonstrated the ability of BNP to identify those at low or intermediate risk of CHD who will develop clinical CV disease. Again the low number of events so far makes it hard to draw any firm conclusions. There was a trend towards more cerebral (stroke) events in those with a higher BNP level and more coronary

events in those with lower BNP levels. Interestingly BNP levels were associated with predicted CHD and CVD risk and increasing age, female sex, ex-smoking status, lower heart rate, lower total cholesterol and higher HDL were all independently associated with BNP levels. This association with traditional risk factors gives some support to evidence from other studies that BNP is associated with CV risk however at this stage it is not clear if BNP is a suitable initial screening test for CV disease particularly to exclude those who will not develop clinical disease who we would aim to reassure that they are truly low risk. As CV events accumulate during continued follow up it may be that a benefit of measuring BNP in predicting CV disease is demonstrated.

We have characterised the normal values and distribution of a range of left ventricular structural and functional parameters derived using a steady state free precision sequence MRI in a population at low or intermediate risk of CHD. Left ventricular mass (LVM) and left ventricular mass index (LVMI) was significantly higher in men than women. Left ventricular end diastolic volume, end systolic volume, stroke volume and cardiac output (including when indexed for body size) were all significantly higher in men compared to women and ejection fraction was higher in women. Age was weakly but significantly inversely associated with LVM and LVMI (except when indexed by $height^{2.7}$) in men but only with LVM and LVM indexed by height in women. These associations persisted in a multivariable regression model suggesting that the association may be independent of other changes in CV risk that accompany age. Age was also associated with decreasing LV volumes, stroke volume and cardiac output in both men and women which persisted when corrected for other variables in the multiple regression models. This may suggest that age specific normal values for MRI derived cardiac measurements may be required.

LVM/LVEDV ratio (a measurement of concentric remodelling) was much more strongly correlated with predicted CHD risk than LVM or LVMI suggesting that concentric

remodelling may be a more important determinant of CV risk than mass alone by differentiating pathologically from physiologically increased LVM.

The vast majority of arterial segments imaged using whole body contrast enhanced magnetic resonance angiography in participants at low or intermediate predicted risk of CHD were normal with no stenosis. Of those that were abnormal most only had a mild stenosis. The standardised atheroma score was positively associated with predicted 10-year CHD risk in men and women. Age, systolic BP, ex-smoking status, heart rate, current smoking status and SIMD decile were independently associated with SAS. The strongest association was with age suggesting this is the greatest driver of the association with predicted CHD risk.

7. Further work

7.1. Further follow up to 20 years

It is planned to continue to obtain further follow up data on hospital admissions and diagnoses, deaths and prescribing at regular intervals with planned analyses at 5, 10 and 20 years from recruitment. As this data becomes available and more CVEs and deaths occur in the cohort it will be possible to determine whether the screening programme using BNP and MRI imaging is able to improve our prediction of CVEs and death.

A number of possible challenges could influence the follow up period. There is an increasing drive to treat more patients in the community and avoid hospital admissions. As the events and diagnoses are detected by contact with hospitals the change in policy could potentially affect the sensitivity of the follow up method. However the nature of cardiac and stroke disease is likely to continue to require contact with hospital at least in the acute phase the change in focus of locus of care is unlikely to significantly affect the accuracy of follow up. Electronic access to GP data would be useful in the future, to ensure complete follow up in this population.

Another possible challenge is that of potential changes in policy about primary prevention. It is possible that offering statins to a wider range of the population (for example over a certain age or those at intermediate risk) may be advised at some point in the near future. This could modulate the effect of a prediction model and reduce the overall event and death rate in the cohort. We may have to repeatedly reanalyse risk as more becomes known providing shrinkage in the truly ‘low risk’ group over time. However the acquisition of prescribing data for the follow up will allow this factor to be incorporated in the data analysis. It may also bring an opportunity to look at the effect of medication on risk. It is likely that a proportion of people who are offered medication

may not take it allowing observational comparisons to be made between those who take medication and those who do not. As this would be observational data and the taking or not taking of CV drugs may be associated with other health behaviours such data would have to be interpreted cautiously.

7.2. Health economics of the technique as a screening programme

If follow up shows that the screening method is efficacious at improving risk detection and therefore potentially improving how we target primary preventive medication the economics of the approach would need to be investigated. MRI scans are a relatively expensive investigation and would need resources that would either need to be increased or diverted from other uses. Analysis of the efficacy once more end points have occurred will help determine how many scans would be required on a population basis to improve risk prediction. The cost of the scanning and blood tests could then be calculated. The comprehensive follow up data including data of all hospital admissions and prescriptions will allow future analyses of hospital usage costs (including investigations) and prescriptions to be modelled.

7.3. A “Scottish Framingham”

The recruitment of a well characterised cohort of the Tayside population including the ability to follow up for future health events and prescriptions gives potential to further investigate the aetiology and progression of cardiovascular diseases. Additionally the development of other diseases which have a vascular component such as dementia can be studied. This makes the study cohort an excellent research resource similar to the Framingham cohort.

8. Publications and Presentations

8.1. Publications

Gandy SJ, **Lambert M**, Belch JJF, Cavin ID, Crowe E, Littleford R, MacFarlane JA, Matthew SZ, Martin P, Nicholas RS, Struthers AD, Sullivan F, Waugh SA, White RD, Wier-McCall JR, Houston JG. Technical assessment of whole body angiography and cardiac function within a single MRI examination. *Clinical Radiology* 2015; 70: 595-603.

8.2. Oral presentations

Magnetic resonance imaging derived left ventricular parameters and association with cardiovascular risk factors – University of Dundee Annual Student symposium, Dundee, 12th June 2015. Awarded prize.

Screening for asymptomatic cardiovascular disease with contrast enhanced MRI: association of left ventricular mass with whole body atheroma burden, cardiovascular risk and B type natriuretic peptide – European Congress of Radiology, Vienna, March 2015.

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10. Appendices

Appendix 1 – TASCFORCE recruitment leaflet

I am interested...please contact me.....

Please tear this slip off and send it to;

FREEPOST TASCFORCE
Centre for Cardiovascular & Lung Biology
Division of Medical Sciences, Mail Box 1
Ninewells Hospital and Medical School
Dundee, DD1 9SY

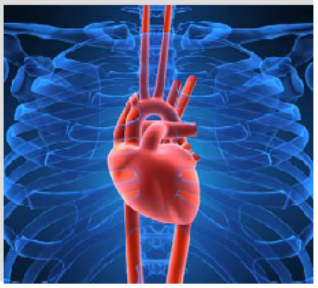
Name: .....

Address: .....

.....

Contact Number .....

E-Mail .....



Contact Information for Volunteers...

Or you can contact the study manager; Roberta Littleford on;

TASCFORCE on 01382 633963

e-mail: tascforce@dundee.ac.uk

We will discuss the project further and send you the full information package for the study.

TASCFORCE is supported by the Souter Charitable Foundation and Chest Heart and Stroke, Scotland.

All your details will remain strictly confidential and will be stored in keeping with the Data Protection Act 1998.

TASCFORCE
Tayside Screening for Cardiac Events

Professor Jill Belch
The Institute of Cardiovascular Research (TICR)
Centre for Cardiovascular & Lung Biology
Division of Medical Sciences, Mail Box 1
Ninewells Hospital and Medical School
Dundee, DD1 9SY
01382 632457
TASCFORCE LEAFLET Version 2 (12th April 2012)

TASCFORCE

Over 40?
At risk of Heart Disease?

Tick the box...
...get checked

Volunteer for the TASCFORCE Project

The TASCFORCE project is a research study headed by Professor Jill Belch at The Institute of Cardiovascular Research at Ninewells Hospital in Dundee.

The project aims to screen 5000 people from Tayside and Fife who are over the age of 40 for early signs of heart and blood vessel disease.

Heart attack and stroke are still amongst the most common causes of illness and death in Scotland.

The project has been designed to screen for early signs of heart disease and to find out how effective our new screening techniques are in predicting the risk of heart disease so that it can be prevented or treated at an early stage.

By taking part in the research study you will have your cardiovascular risk assessed, as well as contributing to medical science and possible future benefits.

E-mail: tascforce@dundee.ac.uk

What is involved?

If you are interested in taking part in the study you will be required to attend Ninewells Hospital for a maximum of two visits. Your travel costs can be reimbursed.

We will give you a mini-health check, which will involve taking your waist measurement, height and weight to calculate you body mass index (BMI) and blood pressure measurements, an ECG (a tracing of your heart) and we will ask you some questions about your medical history.

In addition, we will take a blood sample to measure your cholesterol, blood glucose and BNP levels. BNP is a chemical found in your blood that can indicate how hard your heart is working.

The research staff will give you your results at your visit. Depending upon the level of BNP in your blood, you may be asked to take part in the next part of the study and have an MRI scan of your heart and blood vessels.

The MRI 'pictures' will be examined for any signs of disease.

Call TASCFORCE on 01382 633963

Tick the box...
...get checked

- Over 40 years old ☐
- Not diabetic
- No high blood pressure ☐
- Not taking medicines for high cholesterol ☐
- Never had a heart attack or stroke ☐
- Never had operations for bad circulation ☐

If you ticked all the boxes you may be suitable to take part in the research project.

The Tayside Committee on Medical Research Ethics has examined this proposal and has raised no objections from the point of view of medical ethics.

Call TASCFORCE on 01382 633963

Appendix 2 – Participant information sheet (Cardiovascular risk assessment by BNP)

THE TASCFORCE PROJECT

Tayside **Sc**reening **for** risk of **C**ardiac **E**vents

Participant Information Leaflet No 1 (PIL 1 Version 9)
Cardiovascular Risk assessment by BNP

You have been sent this information sheet because you have expressed an interest in taking part in the TASCFORCE Project. We aim to enroll 5,000 Tayside and Fife men and women into this study. Since you are aged 40 years or over and are not known to have diabetes, hypertension, stroke, heart or blood vessel disease, you may be suitable to take part. Before you decide whether to take part, it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

PURPOSE OF THE TASCFORCE PROJECT

Heart attack and stroke are still amongst the most common causes of illness and death in Scotland, despite major advances in preventive medicine. National guidelines are in place to assess whether an individual is at risk of heart and blood vessel disease, and thus requires treatment. We believe, however, that some people may still be at risk, but that the current methods of assessments fail to detect this. The project has been designed to identify these people, to screen for early signs of heart disease and to find out how effective new screening techniques are in predicting the risk of heart disease so that it can be prevented or treated at an early stage.

The project will be carried forward in two stages:

1. Assessment of cardiovascular (heart and blood vessel) risk.

2. Screening for early signs of cardiovascular disease by Magnetic Resonance Imaging (MRI, heart and blood vessel scan) in those found to be at risk.

At the first stage of the project, we wish to identify those who may be at, as yet undetected, cardiovascular risk by measuring a blood chemical called BNP. The level of BNP in the blood shows how well the heart is working and helps us to assess risk. This information sheet tells you about this first stage of the TASCFORCE project. If you are selected to continue to a further stage a separate information sheet and explanation will be given at the time before asking for your consent for further participation.

How will you know that I may be at risk?

Your blood pressure, weight, height, and levels of blood glucose and cholesterol will be measured. These measurements, along with whether you smoke and have a family history of heart or stroke disease will be used to calculate your risk of developing heart disease. If you are found to be at risk using the standard methods of assessment, we will advise you and discuss what next to do to ensure you receive treatment. If you do not seem to be at risk using standard methods, then we will take a blood sample to measure a substance called BNP which measures risk.

What will I be required to do?
You will be asked to attend for one visit to Ninewells Hospital, or to your GP's surgery, or other suitable place. Your travelling expenses can be reimbursed You will have the opportunity to discuss the study and to receive answers to any questions you may have before being asked to sign a form consenting to take part. This visit is to find out if you are suitable to take part in the study and to assess your risk of developing heart disease.

The study nurse will:

- Ask you about your present and past illnesses and what medicines you are taking.
- Ask you whether you smoke and whether any members of your family have had heart disease.
- Carry out an ECG (this is a tracing of your heart activity).
- Measure your blood pressure, weight, height and waist circumference.
- Take some blood (20 ml - about 4 teaspoons) for various tests. This blood will be used to check your blood glucose and cholesterol level, and your level of BNP. These tests will be done right away at the bedside. The rest of the blood will be stored for future research into heart and blood vessel disease as part of a Bio-bank in the Institute of Cardiovascular Research.
- Give you advice and leaflets on how to change your lifestyle to reduce your risks.
- Take a separate blood sample 9ml for genetic study (optional) if you agree to it. A separate information sheet is attached for the genetic sub-study.

If you need treatment under the current recommendations, we will advise you of this, and arrange for you to see your General Practitioner.

If your level of BNP is raised you will be offered a MRI scan of your heart and blood vessels. This will be explained to you at the time and a separate information sheet will be given to you before asking for your consent. If your level of BNP is low then you will be informed, your participation will be gratefully acknowledged but will not be required beyond this first visit.

We will ask your permission to allow us to receive from or pass on any relevant information to your GP for the duration of the study at 2, 5, and 10 years and for a period up to twenty years beyond the study end. We will ask your permission to receive information on any hospital admissions you may have and their diagnoses and to be notified in the unlikely event of your death for a period of up to 20 years. We would also ask you to allow us to receive information regarding any health problems relating to your heart or blood vessels. This will allow us to assess how effective our screening techniques are in predicting and in preventing heart and blood vessel disease and help increase our understanding of these diseases. This information is gathered from the Scottish Office's Information and Statistics Division (ISD) via the Health Informatics Centre (HIC), University of Dundee. All your information is anonymised.

Will I be given the results of any tests that you do?
If you have given a blood sample for DNA, neither you nor your GP will be given the result. You will be informed of your blood pressure, cholesterol levels, and whether your BNP is high or low.

What are the potential advantages of taking part in the study?
You will have the opportunity to reduce your cardiovascular risk by receiving lifestyle management advice and leaflets on any modifiable risks that you may have. If from any of the tests that we do, we feel you should have further investigation, the results will be sent to your GP so you can be treated according to current clinical practice. There is no guaranteed benefit from taking part in the study but your participation contributes to medical science and possible future benefits.

What are the potential disadvantages of taking part in the study?
Blood sampling: Taking blood can be briefly uncomfortable and can on occasion cause some bruising.

How will my information be stored?
Any information we obtain from you and your health records will remain strictly confidential. Information will be stored securely under conditions in keeping with the Data Protection Act 1998. To ensure confidentiality we will allocate a code (not your name) to your records and to your blood samples. We will keep your personal details (name and address) separate from the information collected but linked by your code. Only individuals directly involved with the study will have access to this information. Reports or publications of research findings will not contain information through which you can be identified. We may be required to allow regulatory authorities, who ensure that research is being carried out in the correct manner, to inspect your records but they will not have access to your name or address.

What if anything goes wrong?
Indemnity is provided by the NHS. The University of Dundee covers any non-negligent harm that occurs due to the design of the clinical trial

What are my rights?
Participation in this study is voluntary and you are free to withdraw from the study at any time without having to give a reason. This will not affect your medical care. If you decide to take part you will be given this Information Sheet to keep along with a copy of the Consent Form that you would be required to sign. If you should ever have any concerns about this study or the way it has been carried out, you should contact:

Dr Roberta Littleford, Trial Manager 01382 383231/633963
Professor Jill JF Belch, Principal Investigator 01382 383092
The East of Scotland Research Ethics Service REC 1 has examined this proposal and has raised no objections from the point of view of medical ethics.

Thank you for taking time to read this information sheet.
One of the study nurses will telephone you in the next week to answer any questions that you may have and to make an appointment for you if you decide to take part.

Roberta Littleford
Trial Manager,
The TASCFORCE Project
The Institute of Cardiovascular Research
Vascular & Inflammatory Diseases Unit
Ninewells Hospital & Medical School, Dundee DD1 9SY
Telephone 01382 383231/633963
E- mail: tascforce@dundee.ac.uk

Appendix 3 – Participant consent form (BNP study)

THE TASCFORCE PROJECT
Tayside Screening for risk of Cardiac Events
Consent Form - BNP Study / PIL No.1 (Version 7)
This form must be completed and signed by the research participant in the presence of someone with knowledge of the research designated by the Principal Investigator.

		Initials
I have read and understood the patient information sheet PIL 1 (Version 6).	Yes □ No □	
I have had the opportunity to discuss the study and to ask questions. All my questions have been answered to my satisfaction.	Yes □ No □	
I understand that my participation in the study is voluntary and that I am free to leave the study at any time without having to give a reason and that this will not affect my medical care in any way.	Yes □ No □	
I have spoken to Dr, Mr. Mrs, Miss _____		
I agree that members of the research team and the regulatory authorities can access my medical records and any information collected during the research project.	Yes □ No □	
I agree that members of the research team can contact both me and my GP about any relevant information pertaining to the study now, and in the future, even if at any point I decide not to continue with the study.	Yes □ No □	
Also,		
I agree that you may receive information on any hospital admissions that I may have now, and in the future, even if at any point I decide not to continue with the study or if you find that I am not suitable to take part.	Yes □ No □	
I agree that the information or blood samples that I provide can be used for future medical research into health, illness and medical treatment. This research will be approved by an Ethics committee.	Yes □ No □	
I agree for the storage of my blood sample as part of the Bio-bank study for up to 10 years.	Yes □ No □	
If eligible, I agree to be informed of a future intervention study.	Yes □ No □	
I agree to give a sample of blood for DNA which can be stored for up to 10 years.	Yes □ No □	
I have read and understood the HEALTHFORCE patient information sheet PIL (Version 2) and if eligible would like to take part.	Yes □ No □	
I agree to the research team contacting me in the future about other research projects.	Yes □ No □	
I agree to take part in the above study.	Yes □ No □	

Participant Name: (Block Letters)
_____

Signature: _____ Date: _____

Tel Contact Numbers: Home _____ Work: _____

Study Nurse Signature: _____ Date: _____

Appendix 4 – Case report form (CRF)

Date of Visit ☐☐/☐☐/☐☐☐☐

Date of Birth ☐☐/☐☐/☐☐☐☐ Age ☐☐ yrs

Sex of Subject ☐M ☐F

Consent for main TASCFORCE project YES ☐ NO ☐ ☐☐/☐☐/☐☐☐☐

Consent for HEATHFORCE 2 sub study YES ☐ NO ☐ Pre-Risk Questionnaire Completed C ☐

Consent for genetic sub-study (optional) YES ☐ NO ☐

INCLUSION CRITERIA FOR TASCFORCE	YES	NO
1 Aged 40years or more	☐	☒
2. No known indication for statin therapy	☐	☒
EXCLUSION CRITERIA		
Has the subject suffered in the past from any of the following:	YES	NO
1 Acute Coronary Syndrome (Unstable angina, Myocardial Infarction)	☒	☐
2. Stable CHD/CVD deemed to require statin therapy	☒	☐
3. Amputation due to severe peripheral vascular/arterial disease	☒	☐
4. Revascularisation central or peripheral	☒	☐
5. Stroke	☒	☐
6. Significant dysrhythmia or angina requiring hospitalization in past 6 months	☒	☐
Does the subject currently have	YES	NO
7. Hypertension	☒	☐
8. Diabetes	☒	☐
9. Heart Failure	☒	☐
10. Family history of hyperlipidaemia requiring drug therapy (genetic sample evidence)	☒	☐
11. Known primary muscle disease	☒	☐
12. Known hypersensitivity or intolerance to statins	☒	☐
13. Acute liver disease or hepatic dysfunction	☒	☐
14. Any illness which would compromise the patient's safety or ability to complete the study	☒	☐
15. Any illness which means that the subject is unable to give informed consent	☒	☐
16. Any metal implants or pacemaker	☒	☐
17. Alcohol abuse problem	☒	☐
Does the subject take	YES	NO
18. Over the counter statins (other HMG-CoA Reductase inhibitors)	☒	☐
19. Drugs associated with rhabdomyolysis in combination with HMG-CoA reductase inhibitors	☒	☐
20. Drugs known to affect lipid levels	☒	☐
21. Lipid regulating drugs	☒	☐
Is the subject	YES	NO
22. Pregnant, breast feeding, not using adequate contraception (if of child bearing potential)	☒	☐
23. Participating in another clinical trial in the past 30 days (other than observational or registry)	☒	☐

MEDICAL HISTORY (Give brief details of all significant illnesses or operations with dates)

System	Yes	No	Dates and Details
CVS	☐	☐	
RS	☐	☐	
GI	☐	☐	
GU	☐	☐	
Endocrine/Metabolic	☐	☐	
CNS	☐	☐	
Dermatological	☐	☐	
HEENT	☐	☐	
Psychiatric	☐	☐	
Locomotor	☐	☐	
Haematological	☐	☐	
Other	☐	☐	

CONCOMITANT MEDICATION CHECKED **(Tick when done)** ☐

(Please complete concomitant medication page)

LAST MENSTRUAL PERIOD (LMP)		☐☐/☐☐/☐☐☐☐	☐ N/A
Premenopausal	☐		
Perimenopausal	☐		
Postmenopausal	☐		

RISK ASSESSMENT

Blood Pressure 1: Systolic ☐☐☐ mmHg Diastolic ☐☐☐ mmHg Pulse ☐☐☐ per minute

Blood Pressure 2: Systolic ☐☐☐ mmHg Diastolic ☐☐☐ mmHg

(If systolic is greater than 145 and or diastolic is greater than 90 refer to GP and exclude from study.)

Total Cholesterol ☐☐.☐☐ mmol/L

HDL Cholesterol ☐☐.☐☐ mmol/L

LDL Cholesterol ☐☐.☐☐ mmol/L

Triglycerides ☐☐.☐☐ mmol/L

Glucose ☐☐.☐☐ mmol/L

SMOKING STATUS:- Never Smoked ☐ 1

Ex Smoker ☐ 2

Current Smoker ☐ 3

If Current or Ex - Average per day Cigarettes ☐☐ Cigars ☐☐ Pipes ☐☐

If Ex Date stopped ☐☐/☐☐/☐☐☐☐

Number of years smoked ☐☐

RISK SCORE ☐☐%

If risk score is ≥ 20% refer to GP and exclude from study but continue to follow up via ISD

Height ☐☐☐.☐ cm Weight ☐☐☐.☐ kg BMI ☐☐.☐

Waist Circumference ☐☐☐.☐ cm If BMI > 25kg/m^2 - eligible for HF2 ☐

FAMILY HISTORY, in 1st degree relative of cardiovascular disease? YES ☐ _____

(Female less than 65 years, male less than 55 years)

NO ☐ _____

ECG PERFORMED YES ☐ NO ☐ Comment: _____

VENEPUNCTURE

Have bloods been done for the following
RECHECK CONSENT FOR DNA

	YES	NO	Comment
BNP	☐	☐	
Biobank	☐	☐	
DNA	☐	☐	

BNP ☐☐☐.☐ pg/mL

On the basis of **BNP** is the subject eligible for the following (please tick **one** box only):

BNP Population ☐ 1
MRI Population ☐ 2

Verbal Consent Obtained for (Information Sheet handed out):

MRI YES ☐ 1 NO ☐ 2 N/A ☐ 3 Date ☐☐/☐☐/☐☐☐☐

Comment:

PHYSICAL ACTIVITY None ☐ 1-2x weekly ☐ Moderate 3-4x weekly ☐ Strenuous 5-7 x weekly ☐

Description:

DIET TYPE

Description:

RISK FACTOR COUNSELLING (BHF LEAFLETS)

Eating for your heart YES ☐ NO ☐ N/A ☐ Comment _____

Physical activity and your heart YES ☐ NO ☐ N/A ☐ _____

Smoking and your heart YES ☐ NO ☐ N/A ☐ _____

Comment:	

POST RISK PERCEPTION QUESTIONNAIRE COMPLETED ☐ **Code** ☐

SIMD = ☐☐

(social index of multiple deprivation)

Tick when done.

☐ GP Letter

Appendix 5 – Participant information leaflet (MRI scan)

THE TASCFORCE PROJECT

Tayside **Sc**reening **for** risk of **C**ardiac **E**vents

Participant Information Leaflet No 2 (PIL 2 Version 3) - MRI study

You have already agreed to participate in the TASCFORCE study. You are now being invited to have a scan of your heart and blood vessels using Magnetic Resonance Imaging (MRI) because at the first stage of the project you were found to have an increased blood level of BNP and may be more at risk of cardiovascular disease than those with a lower level. Before you decide whether to take part, it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information. Ask us if there is anything that is not clear or if you would like more information.

We believe that detection of early signs of heart disease would allow for early treatment and ultimately prevent cardiovascular events (heart attack and stroke). We aim to establish that MRI is an effective screening technique for detecting early signs of heart disease.

The cardiac MRI scan creates 'pictures' of the heart and blood vessels which can be examined for any signs of disease. We have chosen this method of screening because it does not use radiation (like x-rays) and is safe and non-invasive. To ensure that the pictures are clear and to provide information about blood supply to the heart tissues, an injection contrast agent (gadolinium) is given. Gadolinium looks clear like water and is non-radioactive and has been used for many years without serious complications in thousands of patients. A specialist will examine the scans for any signs of disease.

What will I be required to do?

You will receive an appointment either by telephone call, letter or e-mail and be sent directions to attend the MRI department of the Clinical Research Centre, Ninewells Hospital, Dundee. If you are a woman of child bearing potential you will be asked to provide a urine specimen which you can either bring with you (a specimen bottle will be provided) or you could provide a sample at the beginning of your MRI clinic visit. A pregnancy test will be performed to ensure your safety. A positive result will exclude you from having an MRI scan (and eye x-ray if applicable.)

Before your scan you will meet one of the research team who will conduct a quick

check that you are still eligible to have the scan and to consent you. You will then be seen by the radiographer, the person taking your scan, and she/he will help you to complete a checklist about pieces of metal or other objects that might stop you having the scan.

If at Visit 1 you are found to have a history of a penetrative eye injury or exposure to metal fragments in your eye(s) you will be asked to consider having an eye x-ray prior to your MRI scan to establish safety. This can be performed at the main x-ray department at the same visit prior to your MRI scan. You will be taken or directed to the x-ray department. If the radiology staff establishes that you are unsafe to scan you will not have your MRI and you will be free to go. With your consent, we will write to your GP informing them of your MRI safety status, as this information may be of benefit for your future health care needs.

You will then be asked to change into a gown for the scan. After being prepared for your scan, which will involve placing a cannula or small tube into your arm, to give the contrast agent, you will be asked to lie up on the scanning table and then will be moved into the centre of the scanner (the scanner is shaped like a big doughnut). During the scan, which takes around 45 minutes, you will be able to speak to the radiographer. The scan will take pictures of your heart and blood vessels. As the scan is noisy you will be wearing hearing protection. After you have completed the scan you are free to go home. You can drive if you need to. A specialist will examine your scan at a later date for any signs of disease and will measure your left ventricular mass.

This visit should take no longer than one and half hours. .

Will I be given the results of the scan?

Your scan will be examined by a radiologist. Prior to your scan you will be asked to give consent to be informed of any incidental finding found during your scan and agree that members of the research team can contact your GP and make any referral required for further investigation. The necessary steps would be taken for you to be treated according to current clinical practice. If no abnormalities requiring treatment are found, we will send you a standard results letter.

What are the potential advantages of taking part in this stage of the project?

By having an MRI scan, the potential is there to detect established heart and blood vessel disease which may otherwise not have been detected and allows for early management. This project may introduce a treatment phase and we will ask for your permission to be invited into this next phase. There is no guaranteed benefit from

taking part in the study but your participation contributes to medical science and possible future benefits.

What are the potential disadvantages of taking part in the study?

1. **Eye (orbital) x-ray: (If this required and you give consent). This x-ray will be taken when you are either sitting or lying down and will take about 5 minutes to perform. This procedure will involve you being exposed to radiation, but it is low and is calculated to be equivalent to a chest x-ray.**

2. **MRI scanning:** This type of scan is very safe and does not use radiation. Some people, when being scanned, may feel a bit closed in but you will be in constant contact with the person performing the scan and you can come out at any time. The scanner is a bit noisy but you will be given ear protection which also plays music. The insertion of the cannula (needle) for the contrast medium can be briefly uncomfortable and can on occasion cause some bruising.

3. **Contrast Medium:** Gadolinium is the contrast agent used in the cardiac MRI; it provides greater contrast between normal tissue and abnormal tissue in the heart. Gadolinium looks clear like water and is non-radioactive. In a cardiac MRI scan, a contrast agent injected into the bloodstream can provide information about blood supply to the heart tissues. Usually, several scans are taken: one before the contrast agent is injected and at least one after. The pre-contrast and post-contrast images are compared and areas of difference are highlighted. Gadolinium has been used for years without any serious complications in thousands of patients. The FDA declared Gadolinium safe for use in MRI in 1988. A few side effects, such as mild headache, nausea and local burning, and on occasion a slight local skin rash can occur. Very rarely (less than one in a thousand), patients are allergic to Gadolinium. The Gadolinium used in MRI is many times safer than the iodine type contrast used in CT scans.

How will my information be stored?

Any information we obtain from you and your health records will remain strictly confidential. Information will be stored securely under conditions in keeping with the Data Protection Act 1998.

There will be two sets of information obtained after you have had your MRI scan. One set will be the MRI scan images (and/or eye x-ray, if applicable) and the other, the research data obtained from those images The MRI images (eye x-ray) obtained will be stored indefinitely using your name and unique hospital record number within the NHS

clinical system and can be made available to specialist doctors for your future health care needs. Your research data will be stored using a unique study code which is non-identifiable and held on password protected University of Dundee secure databases. Only individuals directly involved with the study will have access to this information. Reports or publications of research findings will not contain information through which you can be identified. We may be required to allow regulatory authorities, who ensure that research is being carried out in the correct manner, to inspect your records but they will not have access to your name or address.

The company who is providing the MRI scanner (Siemens Ltd) may be sent the images in an anonymised form to help them in the future development of the MRI imaging.

What if anything goes wrong?

Indemnity is provided by the NHS. The University of Dundee covers any non negligent harm that occurs due to the design of the clinical trial. Any harm that may occur by the use of medication is covered by the manufacturer under the Consumer Protection Act.

What are my rights?

Participation in this study is voluntary and you are free to withdraw from the study at any time without having to give a reason. This will not affect your medical care. If you decide to take part you will be given this Information Sheet to keep along with a copy of the Consent Form that you would be required to sign. If you should ever have any concerns about this study or the way it has been carried out, you should contact:

Dr Roberta Littleford, Trial Manager 01382 633963

Professor Jill JF Belch, Principal Investigator 01382 632457

Professor Graeme Houston, Consultant Radiologist 01382 632651

The Tayside Committee on Medical Research Ethics has examined this proposal and has raised no objections from the point of view of medical ethics.

Thank you for taking time to read this information sheet.

Roberta Littleford

Trial Manager, the TASCFORCE Project

The Institute of Cardiovascular Research

Vascular & Inflammatory Diseases Unit

Ninewells Hospital & Medical School, Dundee DD1 9SY

Telephone 01382 633963

Appendix 6 – Participant consent form (MRI scan)

THE TASCFORCE PROJECT
Tayside Screening for risk of Cardiac Events
Consent Form - MRI Study / PIL No. 2 (Version4)

This form must be completed and signed by the research participant in the presence of someone with knowledge of the research designated by the Principal Investigator.

		Initials
I have read and understood the participant information leaflet PIL 2 (Version 4).	Yes ☐ No ☐	☐
I have spoken to Dr, Mr. Mrs, Miss _____		
I have had the opportunity to discuss the study and to ask questions. All my questions have been answered to my satisfaction.	Yes ☐ No ☐	☐
I agree to have MRI with contrast.	Yes ☐ No ☐	☐
I agree, if required, to have an x-ray of my eyes prior to MRI scan for MRI safety reasons.	Yes ☐ No ☐	☐
I understand that by undergoing an eye x-ray, the results may exclude me from having an MRI for safety reasons.	Yes ☐ No ☐	☐
I agree that my GP be informed of MRI safety status.	Yes ☐ No ☐	☐
I understand that my participation in the study is voluntary and that I am free to leave the study at any time without having to give a reason and that this will not affect my medical care in any way.	Yes ☐ No ☐	☐
I understand that my identifiable MRI images of my heart and blood vessels will be stored within the NHS clinical system and will be available to specialist doctors looking after me in the future.	Yes ☐ No ☐	☐
I agree (if applicable) to supply a urine sample for pregnancy testing. I understand that a positive result will exclude me from having eye x-ray and MRI scan.	N/A Yes ☐ No ☐	☐
I agree to be informed of any incidental finding found during my MRI scan and agree that members of the research team can contact both me and my GP and inform any referral specialist required to carry out further investigations.	Yes ☐ No ☐	☐
I agree that the images of my heart and blood vessels may be sent to Siemens Ltd in fully anonymised form to aid future development of MRI Imaging.	Yes ☐ No ☐	☐
I agree to take part in the above study.	Yes ☐ No ☐	☐

Participant Name: (Block-Letters)
_____

Signature: _____ Date: _____

Tel Contact Numbers: Home _____ Work: _____

Study Nurse Signature: _____ Date: _____